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CUTANEOUS CARCINOMA MISTAKEN FOR STASIS ULCER OF THE LEG*

KIRKLEY R. WILLIAMS, M.D., AND HARVEY R. BUTCHER, JR., M.D.

St. Louis, Missouri

The determination of the nature of chronic ulcer of the leg cannot be made without biopsy and cultures. The failure to perform a biopsy on chronic indolent ulcers of the lower extremity before treating them as stasis ulcers with unctions and elastic bandages may well lead to the treatment of ulcerated malignant neoplasms of the skin of the leg by completely improper methods. At times ulcerated squamous cell cancers and melanocarcinomas of the skin of the leg resemble stasis ulcers. During the last 5 years we have attended 5 persons who had had malignant neoplasms of the skin of the leg treated with bandages and salves for 3 months to 3½ years before biopsies were performed and the true nature of the ulcer discovered. None of the 4 squamous carcinomas arose in scars and consequently could not be considered as Marjolin's ulcers. They were simply primary cutaneous cancers of the skin of the leg.

CASE REPORTS

Case 1. A 66-year-old man had an ulcer of the skin of the lower left leg appear where a "warty" growth had been for several months. The ulcer was treated by a number of physicians with ointments, salves and dressings for 3 years before we saw him. He had had bilateral varicosities for many years but had not noted dependent edema, cutaneous pigmentation, or thrombophlebitis. The ulcer measured 10 by 15 cm. and was epidermoid carcinoma in its entirety (fig. 1). It was excised on January 23, 1959. The excision included the anterior cortex of the tibia beneath the ulcer because of periosteal neoplastic invasion. The ileofemoral lymph nodes were removed in continuity; 11 of 19 nodes examined contained cancer. A left hemipelvectomy was performed 14 months later in order to control the pain of osseous metastases in the left femur. The pain had persisted despite irradiation and the insertion of an intramedullary nail across a neoplastic defect in the femoral shaft. He is still alive without evidence of persistent neoplasm 1 year and 4 months after the local excision and lymph nodal observation.

Case 2. A woman of 81 years consulted us for a cutaneous ulcer 5 cm. in diameter on the anterior aspect of the right leg (fig. 2). Although she had had no thrombophlebitis, varicosities, dependent edema or cutaneous pigmentation, the area of ulceration had been treated by a physician as a "vascular" ulcer for 2 years. It proved to be all epidermoid carcinoma and was treated by excision on March 1, 1960. The right inguinal lymph nodes which originally were 1 to 2 cm. in diameter have become smaller since the cutaneous autograft healed.

Case 3. A Negro woman 50 years old entered the Barnes Hospital because of an ulcer of the right leg that had appeared 3½ years before and slowly enlarged despite all sorts of local treatment directed. The ulcer and the skin about it were excised and the defect covered with a split-thickness cutaneous autograft. She refused right ileofemoral nodal dissection.

Case 4. A 68-year-old man had an ulcer 5 cm. in diameter that began 3 months before we saw him. It was located on the lateral surface of the lower third of the left leg. He had consulted a physician soon after he discovered the ulcer; however, it had not healed because it was being treated conservatively as a stasis ulcer. A narrow border of induration was present about the ulcer, but no varicosities or cutaneous pigmentation

* From the Department of Surgery, Washington University School of Medicine and Barnes Hospital, St. Louis, Missouri. This study was supported in part by grant H-2569 (C4) from the National Institutes of Health, United States Public Health Service.

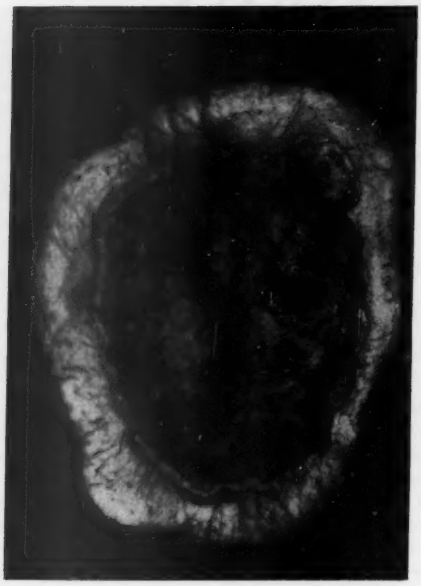

FIG. 1. The photograph shows the epidermoid carcinoma and surrounding skin removed from the leg of case 1. It had been treated as a stasis ulcer for 3 years.

FIG. 2. The photograph shows the epidermoid carcinoma of the skin that had been mistaken for a "vascular" ulcer of the leg for 2 years (case 2).

existed. Biopsy of the ulcer showed it to be an epidermoid carcinoma. The lesion was excised widely.

Case 5. A 54-year-old man developed an ulcer of the right heel in April 1959 after he opened a blister that had followed mild trauma. He was treated 4 months by physicians for what was thought to be a vascular ulcer. Subsequently, biopsy of the ulcer showed malignant melanoma. The lesion was excised widely along with a portion of the underlying oscalcis. An ileofemoral nodal dissection was performed 3 months after the excision of the melanotic ulcer because of the appearance of enlarged femoral nodes. Of 27 lymph nodes examined, 8 contained melanocarcinoma. He is still alive but has persistent melanoma in the right inguinal region.

DISCUSSION

The diagnosis of "stasis" ulcer of the lower extremity is based upon physical signs. These are cutaneous atrophy and pigmentation, subcutaneous and dermal thickening (brawny edema), and varicosities about the ulcer. The cutaneous pigmentation and underlying fibrotic thickening of the subcutaneous tissue may extend 10 or more cm. beyond the edge of the ulcer. If all of these signs are absent in the tissues about an ulcer of the leg, the ulcer is not likely to be of the stasis type.

There is no single pathognomonic symptom or sign, nor any microscopic characteristics which distinguish a stasis ulcer. Only by the elimination of specific causes for persistent cutaneous ulceration can this diagnosis be made with any confidence.

Ulcers of the lower extremity which are the result of specific bacterial, mycotic or parasitic infections may be diagnosed by proper microscopic examination and culture of the exudate. Hemic abnormalities and arterial blood flow deficiency may be contributing causes. When specific infections, arterial blood flow deficiency, blood dyscrasias and iatrogenic ulcer-producing agents have been excluded, the chronic leg ulcer can be considered as a stasis ulcer if its origin is not factitious or neoplastic.

Primary epidermoid carcinoma of the skin of the leg may be mistaken for a stasis ulcer. The only way to distinguish ulcerated neoplasms of the skin of the leg from nonneoplastic ulcers is biopsy. As chronic indolent ulcer of the leg should not be treated without preliminary biopsy, malignant neoplasms are not properly treated with salves and elastic bandages!

PROPHYLAXIS AND TREATMENT OF HYPOTENSION DURING SURGERY AND ANESTHESIA*

JOHN R. S. SHIELDS, M.B., CH.B., AND ROBERT B. DODD, M.D.

St. Louis, Missouri

Probably the most frequent cause of alarm to both the anesthetist and the surgeon during present day operations is a fall in the patient's blood pressure. For a very long time, on too many occasions, there has been a tendency to treat this very important complication by rather empirical methods. Some anesthetists, for example, would always give a vasopressor drug, some would always give a blood transfusion, some would ask the surgeon to stop operating because the patient had become hypotensive, whereas others would implore the surgeon to hurry along with the surgery in exactly the same situation. If the event is analyzed a little more carefully, one will find that in many cases the causes of hypotension fall into definite groups requiring quite specific lines of treatment.

Not all the answers are known, but much has been learned in the past 10 or 15 years. It is, of course, impossible to deal with all of the causes of hypotension but some of the more important ones are listed in table 1. They fall into four main categories.

1. Conditions and Diseases Already Existing Preoperatively

a. Anemia. The optimal, or minimal, hemoglobin level for a patient about to undergo major surgery is not known, but it should probably be above 10 gm. per 100 ml. in the adult. Some anemic patients tolerate anesthesia and major surgery amazingly well without whole blood transfusion during the operative procedure.[19] Most anemic patients, however, should be transfused with whole blood or packed cells preoperatively up to a hemoglobin level at which they can tolerate the expected blood loss at surgery. Ideally, blood transfusion should not be performed at all during general anesthesia; but because of emergency surgery for bleeding and trauma and because of the magnitude of some elective surgery currently being done, blood must be given to certain patients while they are under general anesthesia. In the absence of evidence of excessive blood loss or signs of impending shock, surgical blood loss should be replaced, if necessary, after the patient responds from anesthesia. Thus prevention of hypotension in this instance is having an idea of how much blood loss the individual patient can tolerate, keeping in mind that one of the causes of blood pressure fall during surgery is transfusion reaction. In choosing the anesthetic agents and technique, remember that the very anemic patient has a low tolerance for all types of anesthesia, particularly thiopental (Pentothal) and spinal.

b. Hypovolemia. A normal hemoglobin level, in gm. per 100 ml., does not necessarily indicate that the patient has an adequate amount of circulating hemoglobin, nor does it give much information as to the state of the patient's extracellular fluid compartment. The patient who has lost large amounts of body fluid, such as the patient with unrelieved small bowel obstruction, may have a hemoglobin level which is higher than normal and yet present as bad a risk of hypotension during surgery as the patient who has suffered severe blood loss. The first patient will require fluid replacement with salt containing fluids, whereas the second will require replacement of the formed elements of the blood.[10]

c. Age. The elderly patient with advanced arteriosclerosis may have a much higher initial blood pressure than a patient half his age, but his blood pressure is usually much more labile. Hypotension during surgery in the elderly occurs more frequently regardless of the type of anesthesia used and is, furthermore, much more dangerous than in the younger subject. Prophylaxis against hypotension in this instance requires cautious induction of anesthesia, when general anesthesia is used, judicious use of vasopressors and minimal use of depressant drugs which have to be metabolized by the body.

d. Cardiac and respiratory disease. A discussion

* From the Division of Anesthesiology, Department of Surgery, Washington University and Barnes Hospital, St. Louis, Missouri.

TABLE 1

1. Conditions and diseases existing preoperatively
   a. Anemia
   b. Hypovolemia
   c. Age
   d. Cardiac and respiratory disease
   e. Drugs
2. Effects of the surgical procedure
   a. Position
   b. Blood loss
   c. Vasoconstriction
   d. Pain or visceral stimulation
3. Effects of anesthetic agents and techniques
   a. Overdose of anesthetic
   b. Inadequate anesthesia
   c. Underinflation of the lungs
   d. Overinflation of the lungs
   e. Specific agent effects
4. Intentionally produced hypotension

of which types of cardiac disease constitute the greatest risk during anesthesia and surgery is beyond the scope of this paper. The patient with cardiac disease is mentioned here in a plea for more frequent use of preoperative digitalization of elderly patients who are to undergo major surgery. The older patient may not have heart disease, according to standard clinical criteria, before surgery, but he may not be able to tolerate the effects of the depressant drugs and the shifts in blood volume attendant upon considerable blood and fluid loss and replacement. There is a definite clinical impression at this institution that digitalis protects the elderly heart against failure and arrhythmias leading to failure, particularly tachycardia, during surgery and the immediate postoperative period. This is supported by some laboratory and clinical evidence.[2, 9, 18]

The elderly emphysematous patient with symptoms of chronic respiratory obstruction should certainly be digitalized. His heart is under a chronic strain and the additional strain of anesthesia and surgery may be too much. The emphysematous patient should be brought to optimal condition with the use of preoperative aerosols and bronchial dilators before elective surgery is performed. Unprepared patients of this type have been seen who were unable to maintain a blood pressure or consciousness postoperatively without respiratory assistance. Properly prepared respiratory cripples may tolerate major operative procedures amazingly well.

e. Drugs. Various drugs in common use may affect the patient's blood pressure response to anesthesia. Prominent among these are antihypertensive drugs containing reserpine (Serpasil, Raudixin). It is recommended, when possible, to discontinue reserpine for 10 days to 2 weeks before surgery. When this cannot be done, the anesthetist should be informed of the possibility of a sudden precipitous fall in blood pressure as surgical anesthesia is attained. Clinically, it has been found that atropine, administered intravenously, will reverse many such blood pressure falls.[8] From the mode of action of reserpine, it would appear that norepinephrine (Levophed) is the agent of choice for counteracting the hypotension.[7] Phenylephrine (Neo-Synephrine) and methoxamine (Vasoxyl) are also effective, however.[11]

Adrenal cortical steroids and corticotropin (adrenocorticotrophic hormone) are drugs which profoundly affect the patient's response to anesthesia and surgery. In this instance, the drug should not be withdrawn before surgery. Rather, if the patient has received steroids in significant amounts during the year preceding surgery, he should be fortified with additional amounts of intramuscular cortisone on the day preceding surgery, on the day of surgery and for 4 or 5 days after surgery. The patient should also receive hydrocortisone (Solu-Cortef) in his intravenous fluids during surgery and may need additional hydrocortisone during the immediate postoperative period.[16]

Drugs used in preanesthetic medication may also be causative agents in the production of hypotension. A history of over-reaction or outright sensitivity to depressant drugs should warn against the possibility of this occurring. Barbiturates appear to be the least noxious, although not infallible, drugs for preoperative sedation. Morphine appears to cause fewer blood pressure falls than meperidine (Demerol).[15] Patient response to the tranquillizer group of drugs tends to be unpredictable and their use, at this institution, is at present reserved for special indications in the adult. Promethazine (Phenergan) premedication has been quite satisfactory in children, however.

If a patient should arrive at the operating room with a blood pressure considerably below its normal, anesthesia should be deferred while an effort is made to determine the cause of the

hypotension. It is quite likely that preanesthetic medication is responsible. Such a patient should be observed in the operating room or recovery room to see if his blood pressure returns to normal as the medication wears off. This happens in the great majority of patients. Occasionally, however, careful examination of the patient and his electrocardiographic tracing will reveal that he has suffered an acute myocardial infarction.

2. Effects of the Surgical Procedures

a. Position. Patients under general anesthesia are very susceptible to changes in position. A sudden assumption of a reversed Trendelenburg position, turning the patient to the lateral position for chest surgery or the elevation of the kidney rest are typical examples of position changes that may result in hypotension. The Trendelenburg position itself, if no more than 5 to 10 degrees, may be of great assistance in restoring a patient's blood pressure but it should also be used with caution. This position and the prone position may cause severe limitations of respiratory movement, with resultant detrimental effects on the cardiovascular system, during a long surgical procedure. This is particularly dangerous in the elderly and the obese patient. Assisted respiration should be an essential part of the anesthetic technique in any surgical position which compromises the patient's ability to ventilate.

b. Blood loss. This is one of the most common causes of hypotension during surgery. It is usually accompanied by a progressive rise in pulse rate, though this sign may be masked by the anesthetic or the presence of digitalis. Furthermore, the blood pressure may be kept at an apparently satisfactory level by the stimulation of the surgery, only to fall when that stimulation is withdrawn. In connection with blood loss and its replacement, it should be remembered that massive, rapid transfusion carries with it the danger of citrate intoxication,[4, 5] a syndrome characterized by hypocalcemia, hyperkalemia and an increased risk of cardiac arrest.[12] In such cases it is not uncommon for the patient to remain hypotensive until calcium has been given, after which the blood pressure shows rapid improvement (fig. 1). It is advisable to give 1.0 gm. of calcium chloride intravenously for each 2 or 3 L. of blood administered during rapid transfusion.

c. Vasoconstriction. Shock is a complicated condition. It may present itself in its classical

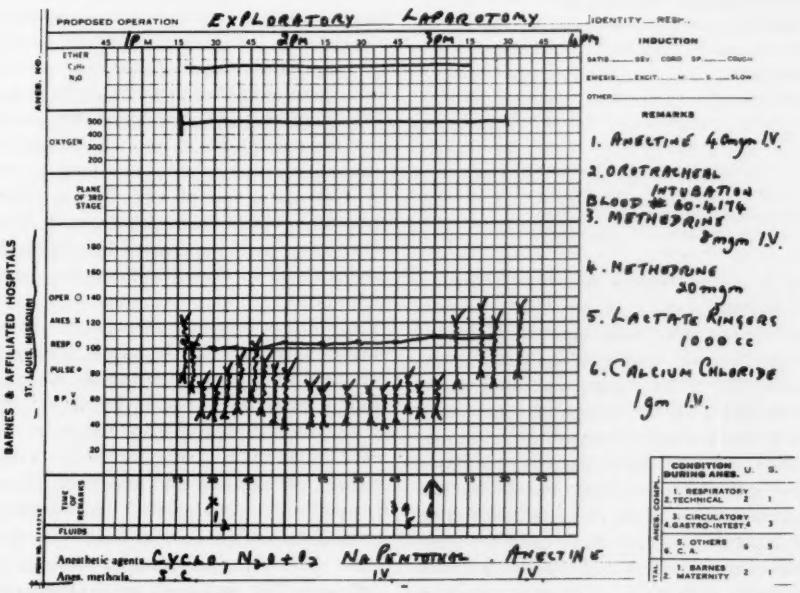

FIG. 1. Patient had received 7 units of whole blood rapidly preoperatively. No calcium salt had been given. Notice rapid response to calcium chloride given at *arrow* after vasopressors had previously failed to raise the blood pressure.

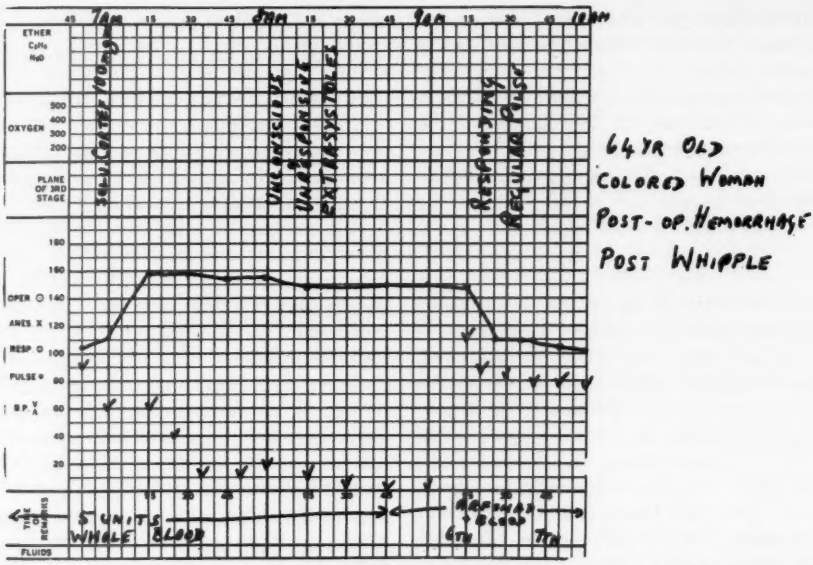

FIG. 2. Chart copied from Recovery Room Record. Notice rise in perceptible blood pressure and improvement in general condition after intense vasoconstriction had been relieved by trimethaphan.

TABLE 2

1. Predominantly *vasoconstrictor*
   a. Norepinephrine (Levophed)
   b. Phenylephrine (Neo-Synephrine)
   c. Metaraminol (Aramine)
   d. Ephedrine
   e. Methoxamine (Vasoxyl)
   f. Hydroxyamphetamine (Paredrine)
2. Predominantly *vasodilator*
   a. Metamphetamine (Methedrine)
   b. Mephentermine (Wyamine)
   c. Methylaminoheptane (Oenethyl)

form of a patient who is hypotensive with a rapid, thin pulse and a cold, moist skin; or there may be a dry skin with obvious peripheral vasoconstriction and cyanosis. The latter is seen particularly in severe burns and after major cardiac surgery, in which the operative procedure has left a much weakened myocardium. It may occur after major general surgery in which there has been extensive dissection and blood loss. The administration of a vasoconstrictor drug, such as norepinephrine, in these cases is contraindicated. The combination of a peripheral vasodilator drug, such as trimethaphan camphorsulfonate (Arfonad), and blood or fluid replacement would seem to be more logical[3] (fig. 2).

At this juncture, it might be well to insert some data from Aviado[1] on the effects of vasopressors on the cerebral, coronary, extremity, mesenteric and renal blood vessels as a guide to the use of these agents. Although one should go to the original article for a more detailed delineation of the drugs' actions, table 2 presents his major findings. The drugs which are predominantly vasodilators produce a rise in blood pressure through cardiac stimulation. Epinephrine has both a vasoconstricting and a vasodilating effect in addition to its potent cardiac stimulating action. The overall effect in man is increased blood pressure and increased blood flow to all organs except the kidneys.

d. Pain or visceral stimulation. Pain from surgery may penetrate the barrier of the analgesia produced by the anesthetic agent. Although this usually produces a rise in blood pressure and pulse, the stimulation may sometimes be sufficient to result in a shocklike state, with hypotension, tachycardia and sweating. This should obviously be counteracted by deepening the level of anesthesia. Careful distinction should be made between this situation and an entirely different state in which surgical manipulation produces a profound effect on the parasympathetic system. Examples of this are frequently

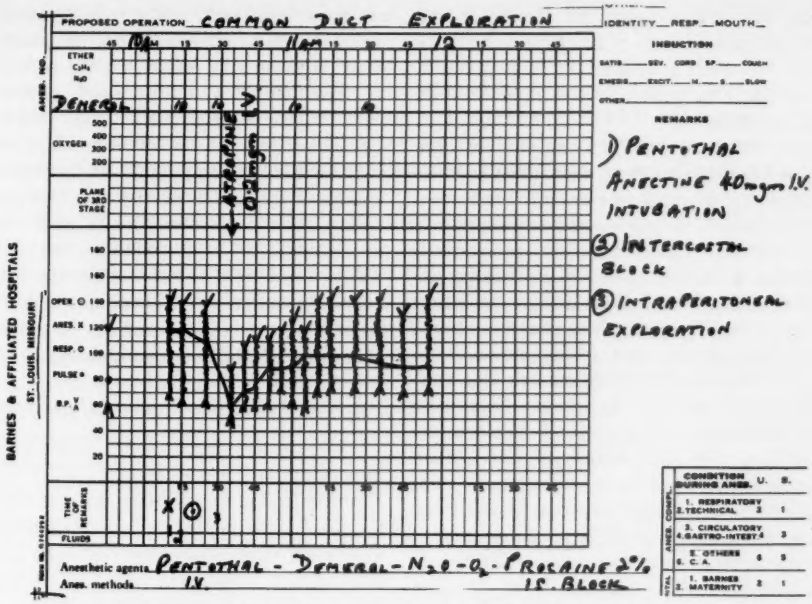

FIG. 3. Notice characteristic fall in blood pressure and pulse accompanied by a decrease in pulse pressure seen with a celiac plexus reflex. This was relieved by atropine given intravenously.

seen when the surgeon pulls on the omentum or when the carotid sinus mechanism is stimulated during dissections of the neck. Such stimulation produces a hypotension which is accompanied by a marked bradycardia due to vagal stimulation. The treatment is withdrawal of the stimulus and, if necessary, atropine intravenously. The improvement is dramatic. (fig. 3)

3. Effects of Anesthetic Agents and Techniques

a. Overdose of anesthetic. This common cause of hypotension may occur with any agent, but is seen most frequently when ether is being used. The causes of the hypotension are many—peripheral vasodilation, direct myocardial depression and sympathetic paralysis are probably the most important. A lighter level of anesthesia will usually result in an improvement in blood pressure.

b. Inadequate anesthesia. Mention has already been made of the fact that inadequate levels of analgesia may result in violent pain stimulation, leading to severe hypotension.

c. Underinflation of the lungs. The immediate result of hypoventilation is accumulation of carbon dioxide. During anesthesia this is not always accompanied by the characteristic rise in blood pressure seen in an unanesthetized man.[14] At the end of the procedure, however, as the patient begins to emerge from anesthesia and breathe more deeply, the excess carbon dioxide is blown off and the blood pressure may fall to dangerously low levels. Hypoxia may also result from underinflation of the lungs and, if persistent, may lead to hypotension or death.

d. Overinflation of the lungs. This may be equally disastrous. A profound diminution of venous return and a consequent fall in blood pressure may result. It is important here to notice the effects of controlled respiration on the blood pressure under different conditions. If the patient's vasomotor system and blood volume are in a satisfactory state, the initial tendency for the pressure to fall when positive pressure is applied will be well compensated for almost immediately. Maloney *et al.*[13] have shown repeatedly, however, that a subject whose blood volume is serously reduced, as from blood loss, may not be able to compensate in response to positive pressure. In such a case, if positive and negative pressure are applied as with a modern automatic respirator, the negative phase may

increase the venous return to the heart and lead to an improvement in blood pressure. This situation can occur so long as the chest is closed, but is unlikely to be seen in the presence of an open pneumothorax.

e. Specific agent effects. It has already been mentioned that all anesthetic agents may produce hypotension if given in excess, but there are a few agents which may affect the blood pressure even before deep planes of anesthesia are reached. Thiopental is one of these. It was shown repeatedly during World War II how dangerous it could be to administer thiopental to patients who were already in a state of hypotension from shock and blood loss. Chloroform has long been recognized to be more dangerous than most agents because of its depressant effect on the myocardium and the blood pressure. Much more recently, halothane (Fluothane) was introduced and, although this has proved to be a very useful agent, there is no doubt that it can very easily result in profound reduction in blood pressure. This probably results from a combination of actions, of which a direct effect on the myocardium[17] and sympathetic blockade[6] are most important, and can be treated with a pressor such as phenylephrine. On many occasions, however, the administration of halothane has resulted in a fall in blood pressure *and* pulse which suggests some vagal effect. This explanation is supported by the excellent response of the patient to atropine. The administration of a spinal or epidural block may lead to tremendous falls in blood pressure. This is mainly due to the sympathetic block produced and should be counteracted by a sympathomimetic drug such as methoxamine or ephedrine, which will be more effective than pressor drugs such as metamphetamine which have some vasodilator effect.

4. Intentionally Produced Hypotension

Three modern techniques in anesthesia are of importance in this discussion.

a. Controlled hypotension, with ganglioplegia produced by trimethaphan camphorsulfonate, is used for a variety of cases, especially in neurosurgery and in massive surgery such as pelvic evisceration, when control of the blood pressure may greatly reduce hemorrhage. Careful atten

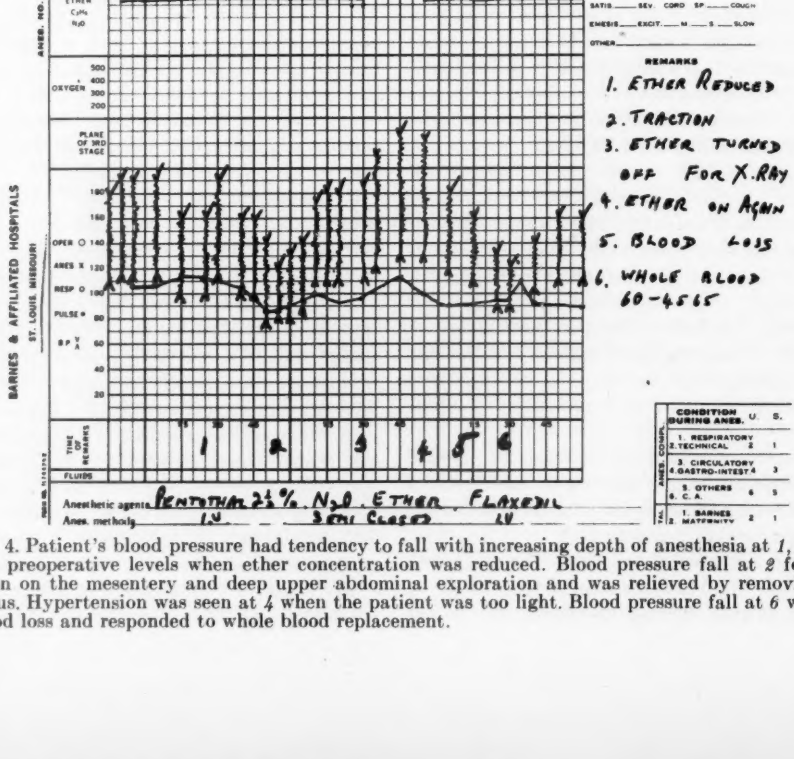

FIG. 4. Patient's blood pressure had tendency to fall with increasing depth of anesthesia at *1*, but regained preoperative levels when ether concentration was reduced. Blood pressure fall at *2* followed traction on the mesentery and deep upper abdominal exploration and was relieved by removing the stimulus. Hypertension was seen at *4* when the patient was too light. Blood pressure fall at *6* was due to blood loss and responded to whole blood replacement.

tion to the maintenance of the blood volume is essential to the success of this technique.

b. More recent still is the use of urea in neurosurgery to reduce the brain volume and tension. The use of this drug produces a tremendous urine output, sometimes in the order of two or three liters in a few hours. It is obvious, therefore, that a severe dehydration may occur which can, in turn, lead to hypotension. Furthermore, if both urea and trimethaphan camphorsulfonate are used in combination, as they may be in some intracranial operations, it may be impossible to restore the blood pressure to normal until the blood volume has been restored.

c. Finally, the modern use of lowered body temperatures, especially in cardiac and neurosurgery, may produce either real or apparent conditions of hypotension. There may be a fall in systemic blood pressure as a result of the hypothermia, which can be very useful in limiting the bleeding during surgery, but there may also be an *apparent* fall in blood pressure due to spasm of the peripheral vessels when the limbs are cold. In this latter circumstance, there may be a perfectly adequate cardiac output and a satisfactory blood flow to the brain and other vital organs. It is necessary to recognize this state because it may be assumed that the administration of a vasoconstricting vasopressor, such as norepinephrine, will probably make the situation worse. The drug of choice, in fact, should be one which will produce vasodilatation, such as trimethaphan camphorsulfonate, or drugs such as metamphetamine or isoproterenol (Isuprel) which will stimulate the myocardium and dilate the peripheral vessels at the same time.

SUMMARY

Hypotension during surgery may be caused by a variety of causes, and the anesthetist should be constantly on the alert for its detection and diagnosis. A careful analysis of the situation can usually lead to a rapid and successful restoration of the blood pressure; neglect of the warning signs may have disastrous consequences.

Figure 4 shows some blood pressure changes, caused by several different mechanisms, which occurred during one operation in an elderly patient. Increasing depth of ether anesthesia caused a slight hypotension in the early stages of the operation. Traction on the peritoneum produced a profound fall in pressure accompanied by a characteristic bradycardia. This situation was reversed when the surgical manipulation was stopped. Later, the ether was turned off entirely for 25 minutes in order that x-rays might be taken. During this period the patient's level of analgesia became too light and hypertension occurred, which was relieved when ether administration was resumed. Shortly after this, another period of hypotension was seen. This was thought to be due to blood loss and responded satisfactorily to a transfusion of 500 ml. of whole blood.

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ANKYLOSIS OF THE JAW FOR TWENTY-TWO YEARS: WITH RESTORATION OF FUNCTION IN SINGLE OPERATION*

JAMES BARRETT BROWN, M.D., AND MINOT P. FRYER, M.D.

St. Louis, Missouri

Ankylosis at the left temporomandibular joint present for 22 years was repaired in one operation with restitution of normal function and improved appearance. Report of this patient and of this procedure is thought important because this particular result may offer hope of relief to others with a similar problem.

The patient gave the history that when she was 2½ years old, infection in the left ear followed measles. There was local swelling with eventual drainage through the ear canal and then subsidence. Ankylosis of the left jaw was progressive so that when the child was 4, lack of motion was quite noticeable.

Various consultants who saw the child through the succeeding years advised no treatment until she was 13, when an operation was done on the joint and a metal plate inserted; 5 months later this plate was removed because of infection. The joint was operated on again by the same surgeon 10 years ago, and another metal plate put in, followed by some function for 6 months. Persistent pain developed in the left temporomandibular joint 5 years ago, and 3 molar teeth were removed after the mouth had been pried open with wedges and a mallet. Resection of the joint was considered, but the patient preferred to wait.

After 5 years the patient was seen here for the first time, having made the best possible adjustment to her deformity through 22 years. Physical signs pointed to a fixation at the left temporomandibular joint. There was deviation of the jaw to that side. A deeper preangular notch could be palpated on the left and there was noticeable flattening of the opposite right cheek. There was no movement of the condyle to be felt on the fixed side. (There is often bony enlargement.) These four signs are important in deciding which joint is involved or mainly involved. The proper side to operate on is sometimes difficult to establish in light of or in absence of exact history. The glenoid region on the left was depressed and there was paralysis of the upper one-third of the face, in addition to the previously mentioned diagnostic signs.

X-ray examination confirmed ankylosis of the left mandible, at the temporomandibular joint. The deep preangular notch and the metal plate in the joint region can be seen in figure 1.

The patient was told resection of the joint offered the best chance of permanent relief from her ankylosis, but after 22 years of fixation soft tissue resistance could interfere with normal opening, and would require long term blocking open of the jaw. Frank discussion with the patient led to understanding and operation.

Operation was done under endotracheal anesthesia. Tracheotomy was avoided by skillful passage of tube blindly into the trachea by Miss Matilda Katterhenry. Incision was made as has been described for parotidectomy[1] and shown in figure 2. Opening was started above the hairline, continued down in front of the ear over the tragus, around under the lobe and down parallel to the jaw into the neck. This flap was reflected forward allowing access to the temporomandibular joint and the jaw itself, to and including the angle. The parotid was elevated and brought forward as was the scarred masseter, after it had been detached from the zygomatic portion of the temporal bone. Extreme care was taken to preserve the 7th nerve, even though traction was needed on the adjacent tissues for the full duration of the operation.

The metal plate (put in at previous operation elsewhere) lying near the joint, shown in figure 1, was lifted out of the operative wound. The joint was involved with thick scar, which was excised, after which the dense bone fixation could be visualized. The condyle, condylar neck and the coronoid process were removed from a solid mass of hypertrophic bone extending throughout the area and far toward the midline under the base of the skull. What produced the wound stimulus necessary for this overgrowth is conjecturable.

The mouth was then opened and further detach-

* From the Plastic Surgery Service, Department of Surgery, Washington University School of Medicine, St. Louis, Missouri.

ment of the mandible from the dense scar tissue was completed through a separate incision inside the cheek. All of the available soft tissue, including the detached portion of the masseter, was placed over the end of the resected mandible. After both incisions had been closed, the mouth was blocked open with a mouth bite and a comfortable pressure dressing was applied.

It is noted that the solid block of bone extended much deeper than the glenoid. There was severe bleeding in under the base of the skull that was controlled with clamps, that could not be safely tied off through the deep small opening. This emergency was met by leaving 6 clamps deep in the wound at the base of the skull and carefully closing around them, and as carefully incor-

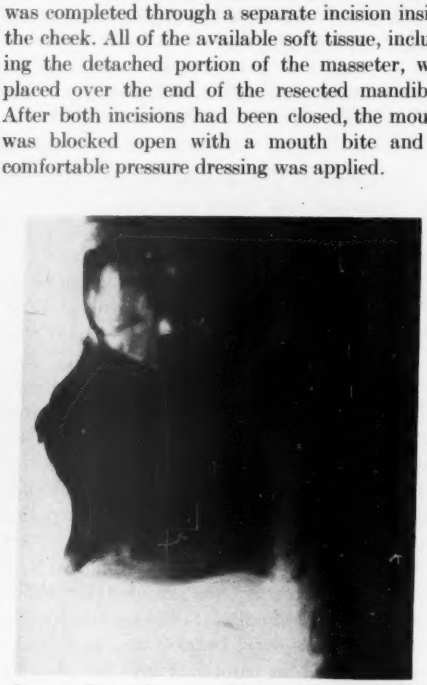

FIG. 1. Lateral x-ray showing bony ankylosis of left temporomandibular joint and metal plate. Deep preangular notch is prominent.

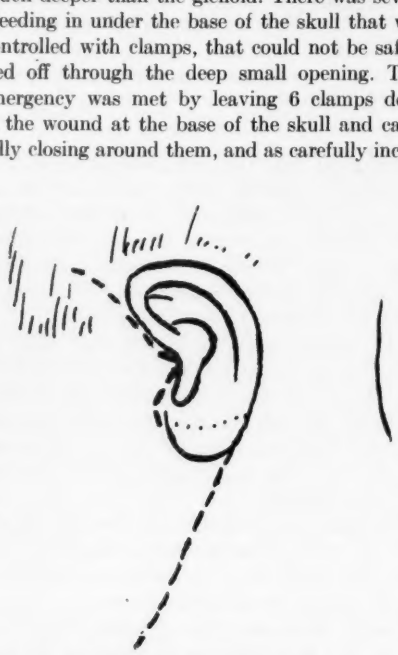

FIG. 2. Drawing of incision giving maximal protection to facial nerve by adequate exposure of operative field.

FIG. 3. *Left*, preoperative efforts to open mouth; *right*, postoperative wide opening

FIG. 4. *Left* and *right*, postoperative open and closed. No damage to facial nerve

porating the clamps in the dressing. These clamps were carefully removed on the 6th day, without further hemorrhage. This simple method of control of hemorrhage in difficult or otherwise hopeless situations, as far as we know, was developed on this service, and has been successfully employed in many instances.

The patient left the hospital 8 days later with the mouth blocked open. Two weeks later she was maintaining a 2½-cm. opening by the intermittent use of blocks between the teeth, and had returned to her normal position in a public office.

Eight months after operation, this patient has a normally functioning jaw—chewing and opening as desired with an unnoticeable scar, as shown in figure 3. An important point in the successful outcome is that a good joint surface has been maintained on the unaffected side.

DISCUSSION

Ankylosis of the mandible at the temporomandibular joint may result from fracture of the condyle, infectious arthritis or any infectious process in that region, as outlined above. Fixation may be due to *soft tissue loss or bone overgrowth.*

Soft tissue fixes by thick scarred bands around the joint or more distant from the ramus or angle to the temporal bone, zygomatic arch or the base of the skull from trauma, infection or sloughing diseases. Scarred or deficient mucosa inside the cheek, as can result from irradiation or cancer removal, is not an uncommon cause. Release and repair is done by excision of the scar and replacement with a free graft, whenever possible, or with local or distant flaps. Such tight binding soft tissue ankylosis may be as rigid as bony ankylosis. Both bone and soft tissue fixation may occur from gunshot and other injuries.

SUMMARY

Report is made of a patient with ankylosis at the temporomandibular joint for 22 years with repair in one operation and restoration of normal function. Discussion of ankylosis of this joint is included.

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ADENOMAS OF THE BREAST: RELATIONSHIP OF ADENOFIBROMAS TO PREGNANCY AND LACTATION

YVON LE GAL, M.D.*

St. Louis, Missouri

True adenomas of the female breast may be defined as benign, well limited epithelial proliferations, with a tubular or tubuloalveolar structure, in which the connective tissue is reduced to the minimum compatible with the nutrition of the neoplasm. Such a definition excludes the following lesions: tubular adenofibroma or pericanalicular adenoma, intracanalicular adenoma and cystosarcoma phyllodes. In these three more common forms of breast adenofibromas, the main component is connective or fibrous tissue. This definition also excludes all benign intracanalicular proliferations and any diffuse hyperplastic process such as adenosis and its variations.

True adenomas are rare; from the figures of Hill and Miller[1] one may expect to find 2 of them in 100 adenofibromas. Nevertheless, they have long been recognized. The first description was written by Velpeau[2] in 1851. In the United States literature, Gross[3] wrote an article in 1897 called "True adenoma of the breast." Most of these older articles are not useful because of the quality of or the lack of illustrations. Recent articles on this subject are few. They may be divided into two main categories. One encompasses studies of tumors of the breast during pregnancy and lactation and, more precisely, the structural modifications of adenofibromas during these periods.[4, 9] Included in the second category are studies dealing with true adenomas of the breast.[1] Hill and Miller describe structural variations with and without pregnancy, but they deny that true adenomas may originate in preexisting adenofibromas. We shall try to reconcile these two concepts by a clinical and morphologic study of our cases.

For this purpose, all the microscopic slides of breast adenomas of unusual structure and all breast biopsies performed during pregnancy and lactation were reviewed, 52 cases in all. Of these 52 cases, 21 showed normal tissue or lesions unrelated to the present study; 7 were common fibroadenomas in which the structure was unremarkable or showed only minimal alterations, and these will be described later; 24 were interpreted as true adenomas belonging to two categories of different importance and significance; of these 24, 3 were so-called apocrine adenomas, and 21 were adenomas of the breast.

* Rockefeller Foundation Fellow.

From the Department of Surgery, Division of Surgical Pathology, Washington University School of Medicine, Barnes and Barnard Free Skin and Cancer Hospitals, St. Louis, Missouri.

APOCRINE ADENOMAS OR SWEAT GLAND ADENOMAS OR HIDROSADENOID ADENOMAS

We prefer the name of hidrosadenoid adenoma, which we have borrowed from Masson,[5] to any other nomenclature. This word is in part derived from the Greek word *hidros* (sweat) and signifies that the tumor is made up of cells morphologically identical to those of the special sweat glands of the axilla. This word is not new; hidrosadenitis has been used for a long time to designate inflammations of these structures. These rare adenomas should not be called apocrine. In the first place, we do not know if they form a secretion and, secondly, if they do, it has not been proved to be apocrine in nature. The best examples of apocrine secretion are the lactating breast and the lactating adenoma. In addition, the hidrosadenoid adenoma is to be distinguished from sweat gland tumors of the skin. The breast adenomas are more deeply situated and of metaplastic origin.

We found two out of a total of three such tumors in patients in their sixties, *i.e.*, in involuting breast parenchyma. This small number illustrates the rarity of this lesion. These adenomas belong to the same group of cellular proliferation as so-called apocrine carcinomas of the breast. The former is the benign neoplasm; the latter the malignant one. We have not been able to find any reference concerning them except a brief one in Masson;[5] furthermore, it deals with dendritic adenomas which we have excluded from this article. The tumors in all of our 3 cases were of small size, about 1 cm. in diameter,

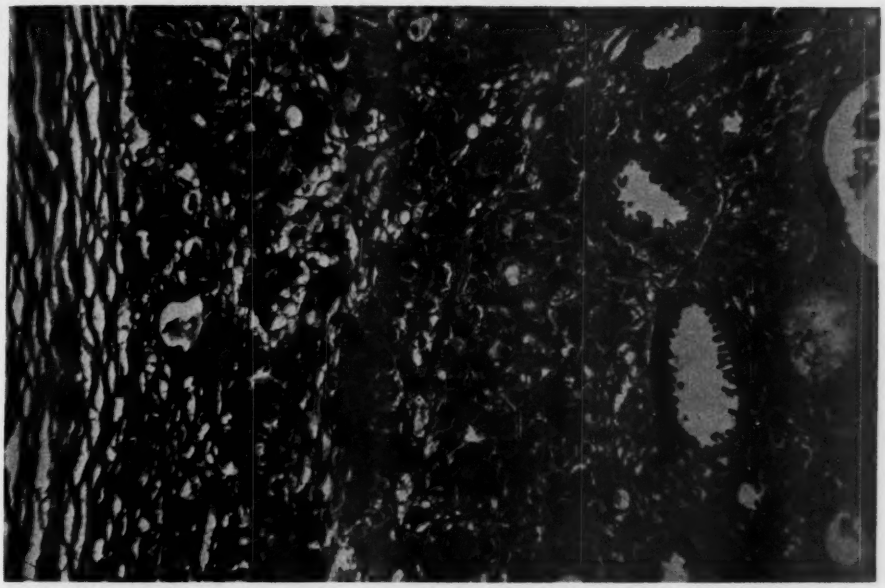

FIG. 1. Hidrosadenoid adenoma, so-called "apocrine" or "sweat gland adenoma." The lesion is sharply delimited. The characteristic acidophilic cells assume a trabecular disposition or form alveoli lined by cuboidal or columnar elements. Patient was a 61-year-old woman (W. U. Ill. 60-3557). Hematoxylin and eosin. 250 ×.

sharply circumscribed and tan in color. They are characteristically composed of acidophilic cells with small round nuclei. The size and the shape of the cells are variable. They are tall with columnar epithelium in well-differentiated tumors or in areas with glandular structures. Their cytoplasm may contain acidophilic secretion droplets (fig. 1). At times the cells are cuboidal or irregular with a trabecular disposition.

TRUE ADENOMAS OF THE BREAST

The main clinical findings of the 21 patients are summarized in table 1. We have divided them into two groups according to their histologic structure. The ages of the patients at the time of operation are known in 19 out of 21 cases; 16 of the patients were between 18 and 30 years of age; 1 was a 9-year-old girl and 3 others were over 30 years of age, with the oldest being 72. These lesions may be located on either side, and may also be bilateral or multiple. The duration of the pregnancy, if any, and the duration of the lump in the breast are given. This study has indicated to us that there is no clear-cut relationship between these data and the histologic structure of the adenomas. Except for the oldest patient, the diagnosis of benign tumor was always made preoperatively.

In considering the origin of these adenomas, some appear *de novo* in a previously normal breast. Case 8 was a 9-year-old child whose breast was certainly easy to examine due to its small size. For this reason, the estimation of the duration of the lesion is reliable. This case has something in common with case 9, a 72-year-old woman. These two tumors occurred at either end of the age span of our cases and are naturally unrelated to any pregnancy. In most instances, one cannot be certain that these lesions appear *de novo*. True adenomas may appear during pregnancy in previously normal breasts (cases 4, 14, 20 and 21). Sometimes the adenoma is noted at the onset of pregnancy (cases 7a, and 18), but in other instances one cannot rule out the possibility that true adenomas are derived from a pre-existing fibroadenoma, for such a fibroadenoma may be small or occur in a bulky or fatty breast, and may never be noticed by the patient. Moreover, there is good clinical and morphologic evidence that an adenofibroma can be completely transformed during pregnancy and lactation. Hill and Miller[1] have not seen it in their material

TABLE 1

True adenomas of the breast

Case No.	S.P.* No., Race, Age	Gravida, Para	Pregnant	Breast	Location	Duration	Size	Comments
					Tubular			
							cm.	
1	59-7304, C, 34	Gravida 7, para 3	5 mo.	Right	Below nipple	2 yr.	6 x 4	After previous pregnancy in 1947; other nodules palpated in opposite breast; has enlarged.
2	52-214, ?, 25		4 mo.	Bilateral	No information	8 yr.	4 x 3 x 2, 1.5 x 1 x 1, 2 x 1, 5 x 1	Left mass noticed 8 yr. ago; right mass noticed 2 wk. ago
3	51-4522, C, 20		4 mo.	Right	Upper, outer quadrant	16 mo.	11 x 7	
4	56-5529, C, 21		7½ mo.	Left	Interior quadrant	3 wk.	2.5 x 0.8 x 1.5	
5	56-1603, C, 23	Gravida 1	8 mo.	Left		4-5 mo.	2 x 3 x 4	Growing
6	55-7124, C, 19		4 days postpartum	Left	Upper, inner quadrant	3 yr.	3, diameter	With focal lactation
7	58-801, C, 19		5 mo.	Right		5 mo.	3, diameter	
7b	59-7305	Gravida 3, para 3	6 wk. postpartum	Bilateral	Several nodules in each breast	16 mo.		Lump noticed in 5th month of 2nd pregnancy
8	38624, W, 9			Right	Above nipple	1 yr.	2 mm.	
9	284, W, 72			Right	Outer quadrant	4 mo.	1.5	
10	31527, W, 25			Right	Outer quadrant	10 yr.	2	Patient received theelin
11	37468, C, 19	Gravida 1	½ mo.	Left		1 yr.	5 x 3. 5 x 3.5	
12	33441, W, 18			Right	Outer quadrant	2 mo.	Walnut	Outside case—slide only
13	41483	Gravida 1	5 mo.	Bilateral	Multiple	2 yr.	5 x 3	
					Lactating			
14	54-2244, C, 28	Gravida 6, para 6	4 days postpartum	Right	Just lateral to areola	Short	3 x 3 x 2	Never noted by patient before
15	54-4950, C, 22	Gravida 3, para 2	6 mo.	Right	Lower outer quadrant		0.5 x 1.5	Duration unknown
16	54-5543, W, 37	Gravida 3, para 2	8 mo.	Right	Lower quadrant		1.7 x 1.5 x 1.2	Duration unknown
17	55-7930, W, 28		5 days postpartum	Left	Unknown	Unknown	6 fragments	Two small identical nodules removed in 1955 at the end of pregnancy
18	56-3899, C, 26		7 mo.	Left		7 mo.	1 x 1 x 1.5	
19	47049, C, 22		5 mo.	Left	Lower quadrant	8 yr.	Small lemon	
20	60-637, C, 25		Postpartum	Right	Upper quadrant	6 mo.	6 x 4 dumbbell shaped	Enlarging even postpartum
21	60-672, W, 22		7 mo.	Left		1 mo.	2	Slightly enlarging

* Surgical pathology.

and deny it, although they describe variations related to pregnancy in their true adenomas. They may not have seen the article in which Moran[4] reported 27 such instances. We have found the various aspects described by Moran and the features illustrated in some of his microphotographs to be identical to our findings concerning the lactating adenomas. However, he did not call them by this name. It is impossible to give an accurate estimation of the importance

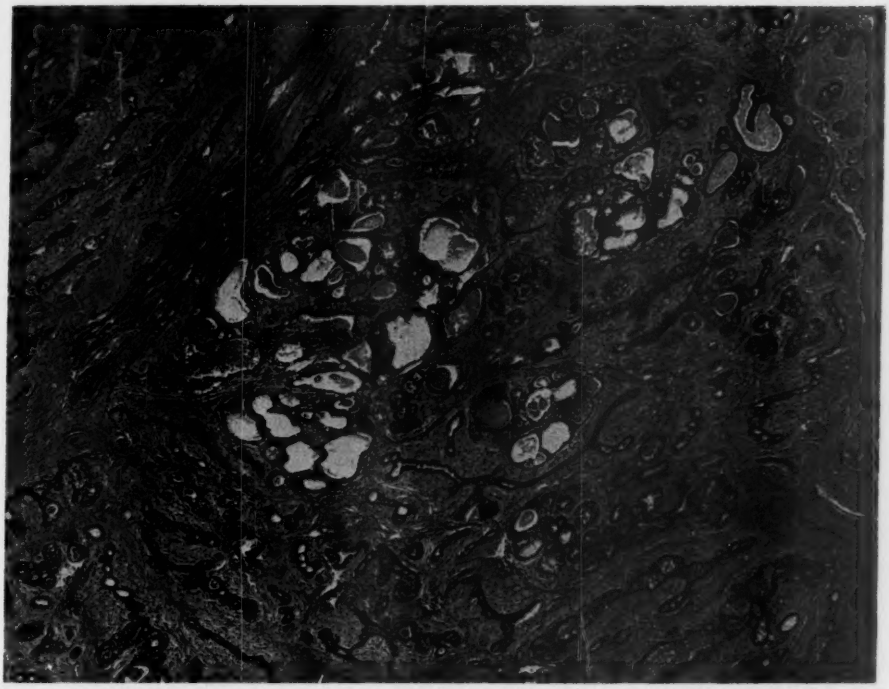

FIG. 2. Abortive pregnancy changes in an adenofibroma of 3 years' duration in a 19-year-old woman, 2 days postpartum. The ductules show some hyperplasia of their lining and some dilations by retention of secretion (W. U. Ill. 60-3561). Hematoxylin and eosin. 40 ×.

of each process: origin *de novo*, or transformation of a pre-existing fibroadenoma. It is obvious that asymptomatic adenomas are not always operated on during pregnancy or at its termination. For the same reason it is impossible to give any estimate of the percentage of fibroadenomas that are transformed during pregnancy and lactation into pure adenomas. This problem is made more difficult by the knowledge that multiple fibroadenomas of the breast in a pregnant woman may have different patterns,[4] and finally that there may be variations of pattern in the same adenoma.

Without forgetting that some adenomas are *de novo* lesions, we will describe the progressive modifications of a fibroadenoma that result in the two main patterns: the tubular adenoma and the lactating adenoma. The epithelial proliferation that occurs in these adenomas is identical to that normally seen in the remainder of the breast in pregnancy, but these two processes are not always synchronous, which is not surprising. The structure of the normal mammary gland is not always homogeneous, whether during a resting phase,[7] or during pregnancy.[4] At the same month of pregnancy, the structure of the adenoma may be tubular or alveolar (table 1).

The simplest and earliest modification is a tubular proliferation combined with some dilation of the ductules of the previous adenofibroma. Its fibrous tissue appears edematous and the collagen is less prominent. The pre-existing ductules are clearly seen and become irregular for a time or even cystic (fig. 2). They are lined by cuboidal and basophilic cells that show only a faint secretory activity. The secretion is a transparent acidophilic liquid with occasional colostrum bodies.

In some lesions the accentuated tubular proliferation is more accentuated (fig. 3). It starts from the pre-existing ductules of the fibroadenoma. The tubes may be of a small diameter with a barely visible lumen and are lined by a single layer of cuboidal and basophilic cells. The number of these tubes shows considerable variation. In many cases they are numerous and are

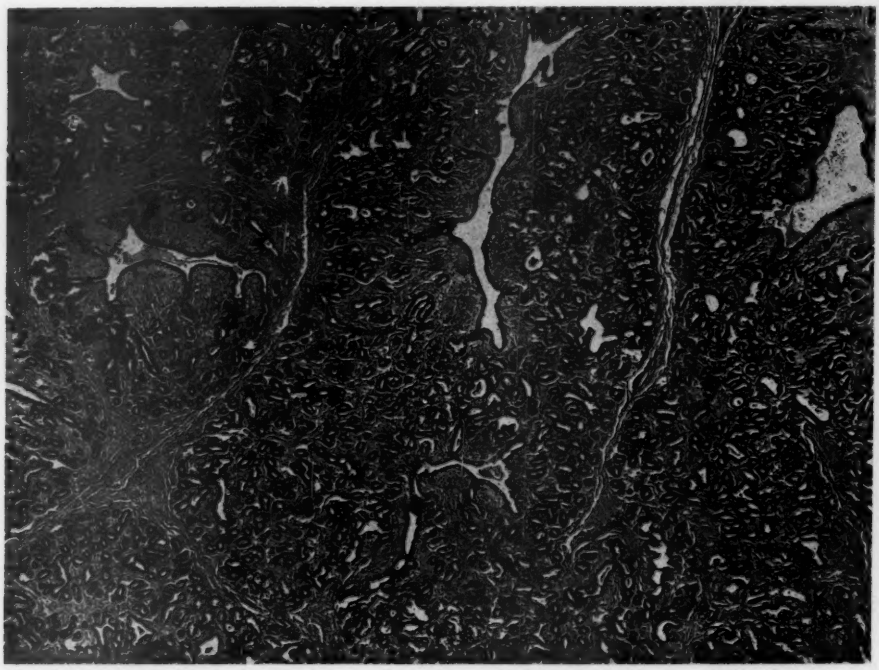

FIG. 3. Pregnancy changes at the 4th month of pregnancy in a fibroadenoma of 16 months' duration in a 20-year-old woman. There is a very active tubular proliferation into the fibrous tissue, starting from the pre-existing ductules. In other parts of the operative material, this tubular proliferation was of the same magnitude as that in figure 4. Hence, this lesion was finally classified as a tubular adenoma (W. U. Ill. 60-3828). Hematoxylin and eosin. 35 ×.

separated one from another by minimal fibrous tissue in which one may find a diffuse lymphocytic infiltration. Such a structure deserves the name of "tubular adenoma" (fig. 4). It has sometimes been called "fetal adenoma," a poor name for a benign neoplasm of the breast of the adult. Let us not forget that some of these tubular adenomas certainly appear *de novo* as a result of localized tubular proliferation in a previously normal breast. In either case, one may suspect that they result from hormonal imbalance comparable to that responsible for all limited or diffuse tubular proliferations of the breast parenchyma, in male or female, such as adenofibromas, adenosis, idiopathic hypertrophy of the breast in the female, or gynecomastia. It is comforting to us to find a tubular adenoma in a patient receiving a synthetic estrogen such as theelin (case 10) because this is the type of lesion one might expect as the end result, if any. We were, however, unable to find any report of experimental adenoma in animals or of true adenoma of the breast in women resulting from administration of theelin.

Whatever their origin, these tubular adenomas are well circumscribed or obviously encapsulated tumors. They may present a certain amount of lobulation, but any one of these lobules is of a greater size than a hyperplastic lobule of a breast in pregnancy.

The color of the gross specimen on cut section is sometimes characteristic; the usual fibroadenoma is white with fine slits or minute holes perceptible when one bends the specimen, but a tubular adenoma is gray or tan because it is made up entirely of glandular tissue. Such a tubular adenoma, unassociated with pregnancy, will maintain the structure described above. But when associated with pregnancy it will, most of the time, undergo changes related to secretion, as the other breast structures do. It may proceed in such a way as to be completed by the fifth

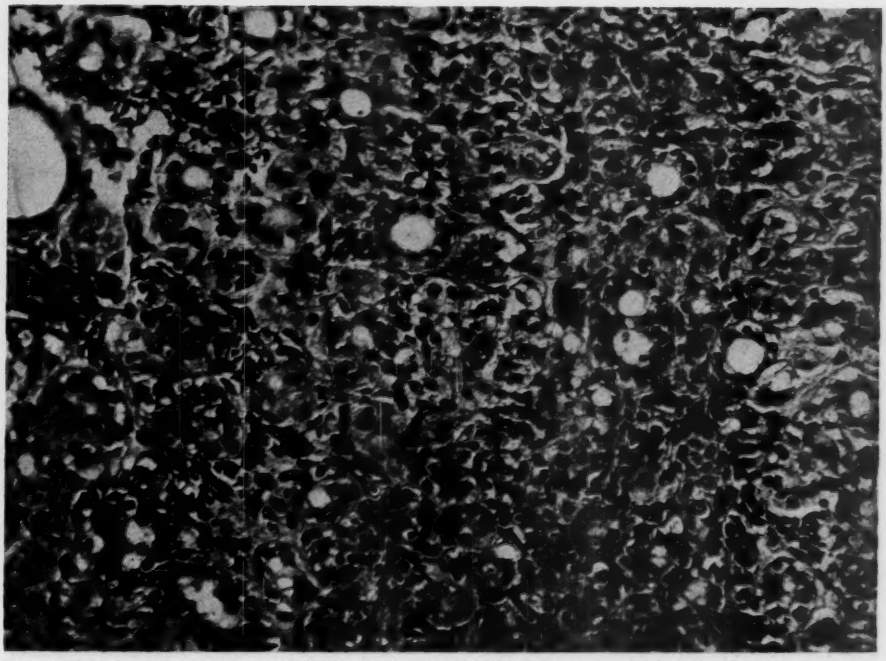

FIG. 4. Tubular adenoma, so-called "fetal adenoma." This lesion may be found at any age and is not always related to pregnancy. It is formed by crowded tubules in a minimal fibrous tissue. Their lumen is barely visible most of the time. There is a slight lymphocytic infiltrate (W. U. Ill. 60-3560). Hematoxylin and eosin. 310 ×.

month of the pregnancy (case 19) or, on the contrary, it may be focal only in the postpartum period (case 6). It may even not occur at all, as in case 7b. The extremities of the ducts are progressively dilated to form alveoli lined by cells with a foamy or vacuolated cytoplasm. The height of the cells varies according to their secretory phases. Sometimes the luminal ends of the cells have disappeared, a characteristic of an apocrine secretion. When these alveoli are not numerous, they appear at low power as minute clear holes in the densely packed and basophilic cells of the tubular adenoma. As they increase in number and diameter, the structure of the adenoma becomes again more homogenous; the ducts are more difficult to distinguish and alveoli predominate (fig. 5). Such a neoplasm deserves the name of tubuloalveolar adenoma or lactating adenoma. But even in this variety, the persistance of some pure tubular areas is not a rare finding. It suggests the ultimate links between the varieties of true adenomas.

The cut section of a tubuloalveolar adenoma is sometimes fairly characteristic in the gross and in full accordance with its histologic features. The tan or light gray of the tubular adenoma is replaced by a yellowish or greasy aspect as the intracellular or intra-acinar secretion products increase. In some cases, a slight pressure on the cut specimen yields a milky oozing or discharge (fig. 6). Hence, the alternate name of lactating adenoma. These lesions are well delimited or even encapsulated as most benign neoplasms are. The largest ones are sometimes described as pear shaped. The intermingling of gray and yellow colors may suggest necrosis in the gross specimen but in reality represents only fat. Areas of necrosis are present but are small and are seen only microscopically. They are of the aseptic type and were found in 2 of our cases (fig. 7). Large zones of necrosis have recently been described in lactating breasts by Hasson and Pope.[8] These authors consider them infarcts. Other times one may find acidophilic zones resulting from some

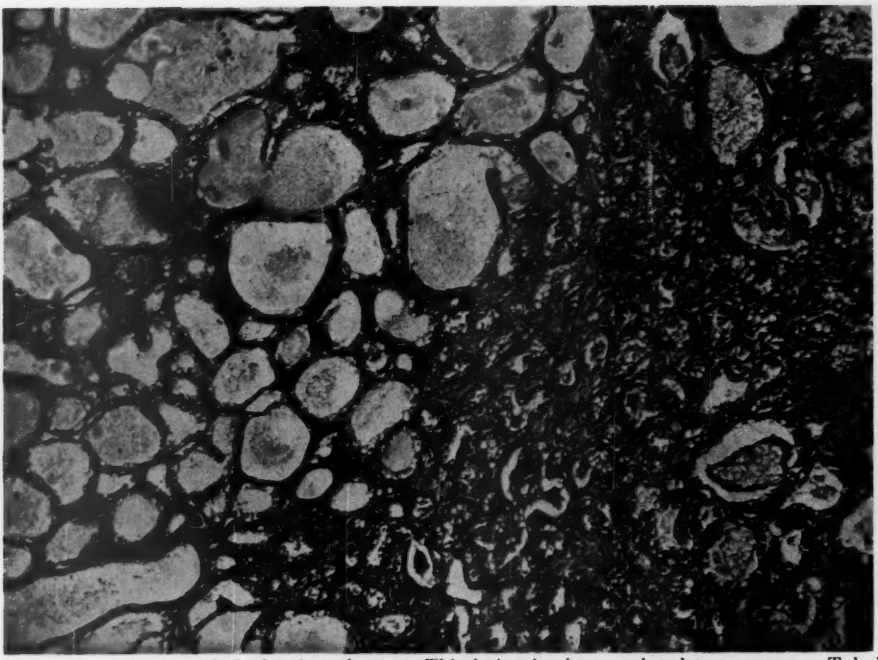

FIG. 5. Lactating or tubuloalveolar adenoma. This lesion is always related to pregnancy. Tubules and above all alveoli, which are of varying sizes, show definite milk secretion (case 20 same as in fig. 6; W. U. Ill. 60-3558). Hematoxylin and eosin. 86 ×.

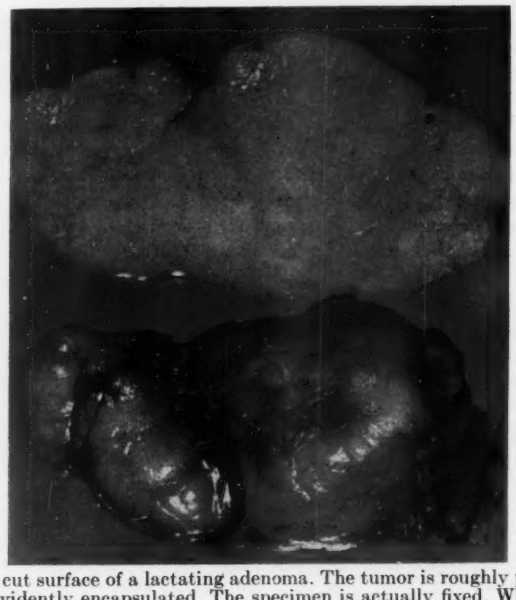

FIG. 6. External and cut surface of a lactating adenoma. The tumor is roughly pear shaped and somewhat lobulated. It is evidently encapsulated. The specimen is actually fixed. When sectioned fresh, it was more pulpy with a milky discharge (same case as in fig. 5; W. U. Ill. 60-771).

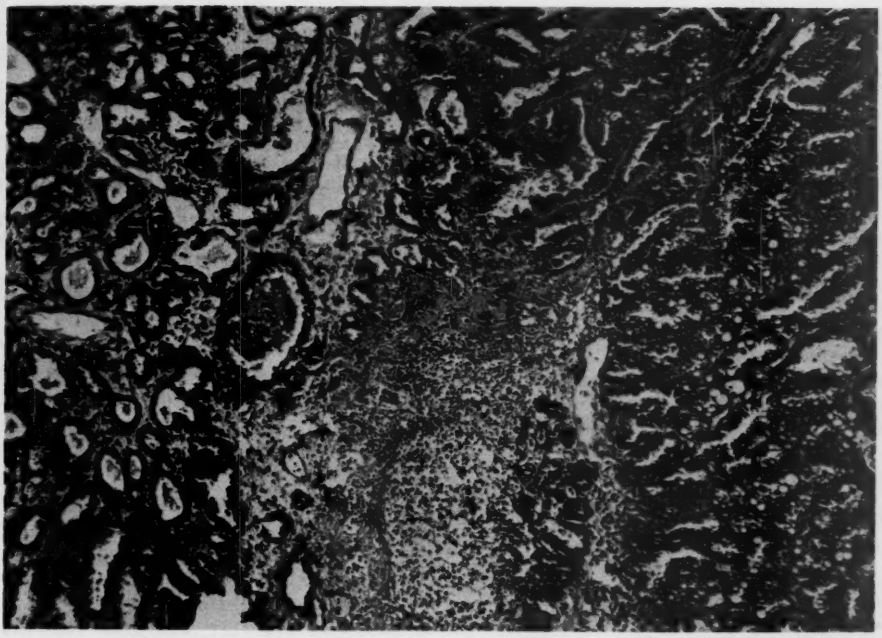

FIG. 7. Focal aseptic necrosis in a lactating adenoma. Besides this peculiar aspect, the structure of the adenoma is characteristic with tubular and alveolar structures showing active secretion (case 21, W. U. Ill. 60-3556). Hematoxylin and eosin. 86 ×.

extravasation of the milky secretion. In spite of the cellularity of these adenomas, the lymphocytic infiltration and the irregularity of the cells in the lactating type, their diagnosis is not a difficult one. They never aroused any doubt clinically or histologically as to their benignancy in our series except in the case of the 72-year-old woman (case 9). However, true lactating adenomas should not be confused with hyperplastic mammary lobules during pregnancy or with residual lactating acini after weaning,[7] for involution can be delayed or even missed in a lactating adenoma.[4] Hyperplastic mammary lobules and residual lactating acini, however, are of a smaller diameter than an adenoma and are divided by larger strands of connective tissue than the few fibrous septa of an adenoma.

SUMMARY

True adenomas of the breast are very rare. This is a report of 24 cases seen at the Department of Surgical Pathology, Washington University Medical School, with an attempt at classification.

Three were hidrosadenoid adenomas, so-called sweat gland or apocrine adenomas. They are formed by large acidophilic cells of metaplastic origin.

The 21 other cases belong to two varieties related to one another: the the tubular adenomas and the tubuloalveolar adenomas or lactating adenomas. The tubular adenomas (so-called fetal adenomas) are usually found in association with pregnancy, but two of our cases (cases 8 and 9) and two of the eight cases of Hill and Miller were unrelated to pregnancy. The lactating or tubuloalveolar form are always related to pregnancy. Both varieties may be *de novo* lesions or may result from a glandular proliferation within a previous fibroadenoma, identical to but not synchronous with the proliferation occurring in the surrounding glandular parenchyma. This lack of synchronism, and possible process of involution in adenomas operated upon postpartum, explains the lack of relationship between the duration of the tumor, its structure and the month of the pregnancy. The diagnosis of true

adenomas is not a difficult one, and they are always recognized as benign.

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THE GROWTH OF A COLONIC ADENOCARCINOMA*

JOHN S. SPRATT, JR., M.D., AND LAUREN V. ACKERMAN, M.D.

St. Louis, Missouri

Theoretically, the growth of a cancer should approach

$$V = V_0 e^{bt}$$

(V_0, the original volume; V, the volume at time t; e, the base of the natural (Napierian) logarithms; t, the time lapse between the V_0 and V; and b, the regression coefficient that characterizes the growth of the particular cancer).[1, 4] To apply this formula to the growth of any neoplasm requires that only one assumption be made; namely, that cancer cells divide at a randomly steady rate and consequently that the growth of the cancer obeys the compound interest law: *that the increase in size of a cancer at any moment is proportional to the size it has already attained.* The mean length of time required for the division of all the cells of the cancer has been designated as the "doubling time" of the cancer. Collins *et al.*,[2] using roentgenographic mensuration, ascertained that the doubling time of pulmonary metastases from rectal cancers borne by 4 people varied between 49 and 123 days, for the most rapidly and the most slowly growing metastases, respectively. However, no data permitting an assessment of the growth rates of primary colonic cancers have been collected. Recently, quite by chance, an opportunity presented itself to ascertain the growth rate of a colonic cancer during 7½ years.

CASE REPORT

L. S. (B. H. no. 212931) was born in Russia in 1885. His colon was first examined roentgenographically August 14, 1952. A polypoid filling defect (2.9 cm. in diameter) was found in the mid-descending colon. On August 19, 1952, a left colectomy was performed and the intestinal continuity was restored by colocolostomy between the mid-transverse and the midsigmoid colon. The tumor was a well differentiated adenocarcinoma with no metastases in 15 mesocolic lymph nodes. A small round filling defect located in the right transverse colon was not removed. Eight subsequent barium enemas performed during the subsequent 7½ years demonstrated growth of this lesion (fig. 1). By January 29, 1960, the tumor had encompassed the bowel and had extended 27 mm. longitudinally. On February 10, 1960, a resection of this still asymptomatic tumor was performed. It was an adenocarcinoma arising in the transverse colon, 6 cm. proximal to the old anastomosis. No gross intra-abdominal or hepatic metastases were found.

This cancer is shown in figure 2. It was a flat, spreading, rodent plaque of cancer, 50 mm. in circumference and 27 mm. in length. Its thickness was uniformly 5 mm. The tumor (no. 60-1075) was well differentiated and its deep surface extended through all layers of the muscular wall and just into the mesenteric fat. No metastases from this cancer were found in 16 lymph nodes removed from the adjacent mesocolon.

One might wonder what his doctors could have been thinking to let this cancer grow for 7½ years before removing it. The reason is simple. During all of these years the man's physical condition was poor. He had had a myocardial infarction during the 5th postoperative day, August 24, 1952. He was obese, hypertensive, had cholelithiasis and prostatism that required a transurethral resection (1954), and he was an old man.

DISCUSSION

Small well differentiated adenocarcinomas (fig. 3) of the colon grow predominantly as plaques. While quite small, the plaques may wrinkle over their submucosal stroma and may even develop pedicles making them grossly indistinguishable from pedunculated benign adenomatous polyps.[5] Later the central part of the plaque erodes while the cancer grows beneath and around the erosion with a tendency toward circumferential spread. The first cancer removed from L. S. in 1952 was also an erosive convoluted polypoid plaque (fig. 4). Consequently, the volume of such a cancer can be calculated from the roentgen films after correcting for magnification simply by treating the lesion as a

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From the Department of Surgery and the Division of Surgical Pathology, Washington University School of Medicine, St. Louis 10, Missouri.

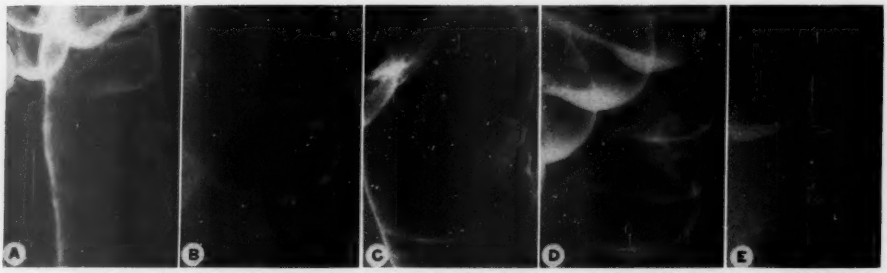

FIG. 1. Photographs of the tumor on 5 of the 9 barium enemas performed on L. S.: *A*, February 11, 1953; *B*, December 5, 1955; *C*, January 4, 1957; *D*, January 8, 1958; and *E*, January 29, 1960. The roentgenograms are on file at the Mallinckrodt Institute of Radiology and at the office of Dr. Wendell G. Scott.

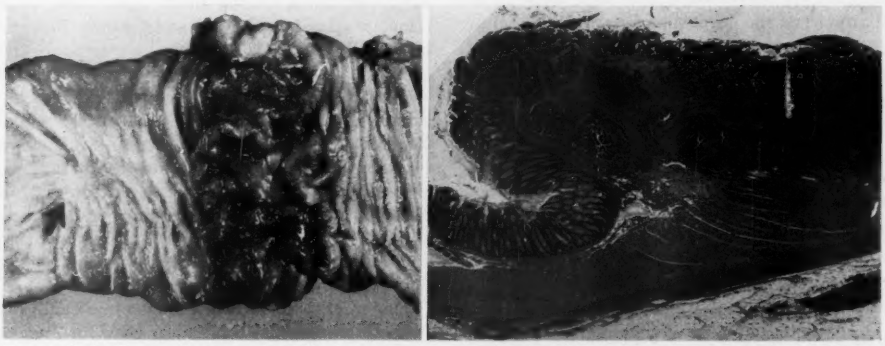

FIG. 2. *Left.* Gross photograph of L. S.'s transverse colonic adenocarcinoma resected on February 10, 1960. The *arrow* points to scarring of the bowel persisting from left transverse to midsigmoid colocolostomy effected on August 19, 1952. *Right.* Photomicrograph of the cancer.

cylinder having a diameter (d) ascertained from the roentgenogram and a depth (h) equal to the thickness of the tumor measured after its removal (table 1).

Correction for the roentgen magnification of the diameter of the tumor could be effected, because all roentgenograms had been taken with essentially the same radiographic technique, by using the following equation:

$$\text{Actual tumor diameter at } x \text{ time} = (\text{roentgen diameter at } x \text{ time}) \times \frac{(\text{actual diameter of the resected cancer})}{(\text{diameter of the cancer on the roentgenogram taken just before resection})}$$

Fortunately, in 3 of the barium enemas taken at Mallinckrodt Institute of Radiology by the same technique in 1952 and 1953, the ratio of actual size to roentgen size (0.86) could be determined from the size of L. S.'s first tumor on the barium enema of August 14, 1952 (2.9 cm.) and the actual size of the freshly removed tumor on August 19, 1952 (2.5 cm.). All of the remaining 6 barium enemas were performed with similar techniques in the office of Dr. Wendell G. Scott (1953 to 1960). The extension of the tumor along the long axis of the bowel was 27 mm. on the barium enema of January 29, 1960, and on the freshly resected colon of February 10, 1960. Consequently, no correction for magnification of the 6 barium enemas made by Dr. Scott was necessary.

The plot of these volumes on a logarithmic ordinate and the corresponding time on a linear abscissa (two-cycle semilogarithmic graph paper) is practically linear (fig. 5) suggesting that there is an exponential relationship between time and volume. However, additional computations are necessary to determine the line of best fit and to establish that there is a significant correlation

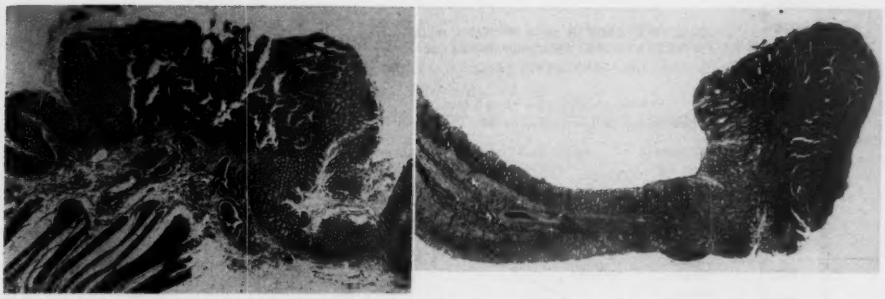

FIG. 3. *Left.* A superficial sessile plaque of well differentiated colonic adenocarcinoma. *Right.* A superficial, pedunculated plaque of well differentiated colonic adenocarcinoma bowed over its submucosal stroma (from Massachusetts General Hospital, courtesy of Dr. Benjamin Castleman).

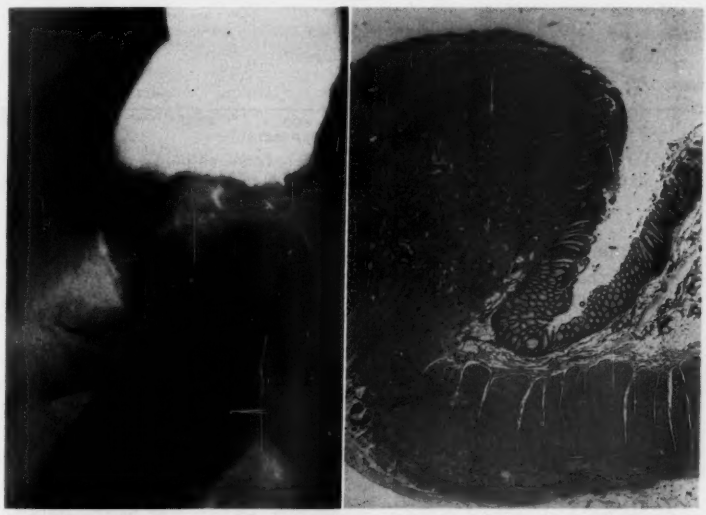

FIG. 4. *Left.* Radiographic image of L. S.'s adenocarcinoma of the descending colon resected on August 19, 1952. *Right.* Photomicrograph of the polypoid cancer resected on August 19, 1952.

between time and volume. By converting the exponential growth equation to its logarithmic form (a linear equation) it is possible to apply the method of least squares of linear regression analysis for determining the line of best fit and the coefficient of correlation as outlined in table 1.[3, 4] The computations contained in table 1 were confirmed by programming the observed data on the Washington University IBM 650 computer with the assistance of Mr. Kenneth S. Barten, director of the computer center. As shown in table 1, there is a highly significant correlation between the volume (logarithmic function) and the duration of the cancer.

Furthermore, as Snedecor[4] has pointed out, the regression coefficient of a growth curve represents the relative rate of growth. The rate of growth of this cancer was, therefore, 0.001089 cu. mm. per cu. mm. of existing cancer per day. Expressed in terms of cells having a mean volume of 1000 cubic microns (10^{-6} cu. mm.), this rate was equivalent to an increase of 1 cell per 1000 existing cancer cells per day. The cellular content of the cancer was randomly doubled every 636.5 days.

If it is assumed that the growth of this cancer was as steady from its beginning as it was during the past 7½ years, the possible age of this tumor

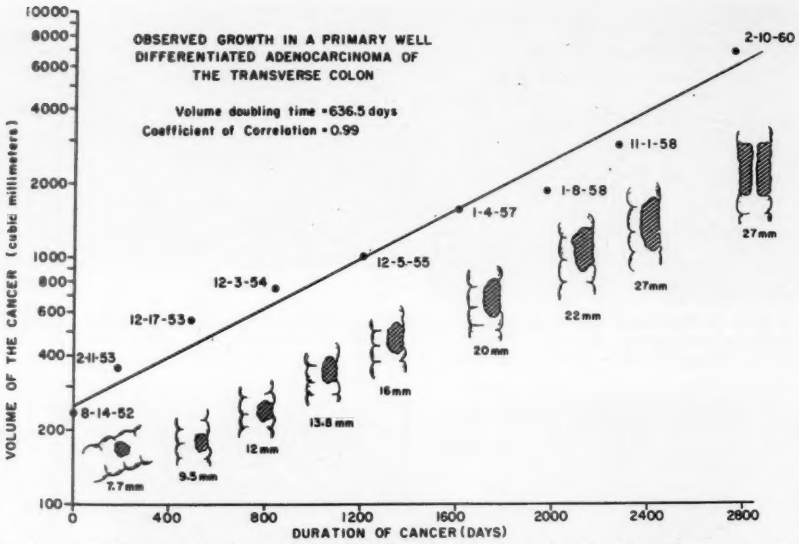

FIG. 5. Observed increases in the volume of L. S.'s transverse colonic adenocarcinoma plotted on a two-cycle semilogarithmic scale with proportional drawings of the tumor as demonstrated on barium enema.

is calculable by assuming that the initial volume (V_0) of the cancer is that of a single cell, 10^{-6} cu. mm. Its final volume (V) (February 10, 1960), was about 6750 cu. mm. The duration is then determined by the following steps:

$$t = \frac{\log_e V - \log_e V_0}{b}$$

$$t = \frac{8.81729 - (-13.81551)}{1.089 \times 10^{-3}}$$

t = 20,783 days or 56.9 years

Certain questions naturally arise. For instance, does not necrosis of the tumor vitiate the true calculation of growth rate? Microscopically, there was no necrosis in this cancer. Does not the desquamation that continually takes place from the tumor render calculation of growth rate superfluous? Unless desquamation is cyclic, it does not seriously affect the calculation. In a cancer having a uniform thickness of 5 mm. and being composed of cells with diameters of 10 microns, only $\frac{1}{500}$ of the cells of the cancer is exposed for possible desquamation. In a cancer growing as a plaque, the rate of desquamation must be constantly related to the total number of cells on the surface of the cancer and the number of these cells is constantly related to the total number of cells in the cancer. Consequently, desquamation proceeds according to the exponential growth equation but with a negative regression coefficient, $-b$. The regression coefficient determined from the observed growth of L. S.'s cancer therefore represents the algebraic sum of the regression coefficient of actual growth, $+b$ and the regression coefficient of desquamation, $-b$. Consequently, mensurable growth (actual growth less desquamation) is still exponential.

A visible concept of the exponential growth can be readily provided by the following analogy. Permit a penny to represent 1 cancer cell; place the penny on the first square of a checkerboard. After 636 days place 2 pennies on the second square, 636 days later place 4 pennies on the third square and continue the process of doubling the pennies placed on each subsequent square every 636 days until the 34th of the 64 squares on the checkerboard is covered. It is this 34th square that represents the actual number of doubling requisite to provide a tumor growing as L. S.'s did to attain the number of cells in his tumor when it was removed [32.65 (the actual number of doublings) + 1 (for the first undoubled

TABLE 1

The growth of a primary well differentiated adenocarcinoma of the transverse colon with computation of the regression coefficient and the coefficient of correlation for the measurements of the volume and the duration of the tumor

Date of Observation	X Days of Observation (t)	Diameter of cancer (mm)	Calculated volume, mm^3 (V)**	Y Natural logarithm of the volume ($\log_e$ V)
14 Aug 1952	0	7.7	232	5.44674
11 Feb 1953	181	9.5	355	5.87212
17 Dec 1953	490	12.0	565	6.33653
3 Dec 1954	841	13.8	771	6.64769
5 Dec 1955	1208	16.0	1005	6.91273
4 Jan 1957	1603	20.0	1570	7.35884
8 Jun 1958	1972	22.0	1900	7.54961
1 Nov 1958	2268	27.0	2863	7.95863
10 Feb 1960	2734	50x27x5*	6750	8.81730

* Dimensions of the unfixed cancer

** First eight volumes computed from $V = 1/4\ \pi d^2 h$, d = diameter, h = 5 mm, accuracy does not exceed two significant figures.

Basic growth equation $V = V_o e^{bt}$

Logarithmic form (linear) $\log_e V = \log_e V_o + bt$

Standard linear equation $Y = a + bX$

$Y = \log_e V$

$a_{yx} = a$ (The Y - intercept) $= \log_e V_o$

b_{yx} (Regression coefficient) $= b$

$X = t$

$$b_{yx} = \frac{n\,\Sigma XY - (\Sigma X)(\Sigma Y)}{n\,(\Sigma X^2) - (\Sigma X)^2} = .001089 \text{ days}^{-1}$$

$a_{yx} = \bar{Y} - b_{yx}\,\bar{X} = 5.62200$

(or V_o, The Y - intercept = 276 mm^3)

Line of best fit by linear regression analysis:

$\log_e V = 5.62200 + (.001089)(t)$

or $V = 276e^{.001089\ t}$

r_{yx} = coefficient of correlation

$$r_{yx} = \frac{n\,\Sigma XY - (\Sigma X)(\Sigma Y)}{\sqrt{n\,\Sigma X^2 - (\Sigma X)^2}\ \sqrt{n\,\Sigma Y^2 - (\Sigma Y)^2}}$$

$r_{yx} = 0.99$

Number of degrees of freedom (for linear regression) = n - 2 = 7

CONCLUSION: The hypothesis that the observed volumes of the cancer bear a logarithmic relation to the duration of the cancer is acceptable with probability greater than 0.98***

***Table IV of appendix, Introduction to Modern Statistics, W.Z. Hirsch, pp 266 and 400 (3)

square of the checkerboard) = 33.65 or approximately the 34th square]. The pennies dropped or desquamated along the way would hardly affect at all the total number of pennies accumulated Actually, 6,750,000,000 pennies ($2^{32.65}$) or $67,500,000 worth of pennies would be found on the final square. In the same way the volume of L. S.'s cancer made up of cells 10^{-6} cu. mm. in size after 56.9 years of randomly doubling would have attained an approximate volume of 6,750 cu. mm. containing about 6,750,000,000 cells when it was removed on February 10, 1960.

That this cancer was of submacroscopic size for about 7 times as long as the 7½-year period of radiographic observation is entirely possible. "Early" diagnosis of this cancer would have been a fallacious concept.

SUMMARY

The purpose of this report is to record a case of exponential growth in a primary colonic adenocarcinoma confirmed on 9 observations in a 7½-year period and to define the method of determining the regression coefficient and the

coefficient of correlation from the mensurable data.

The growth equation for the cancer was $V = V_0 e^{0.001089t}$ equivalent to a "doubling time" of 636.5 days. The coefficient of correlation between the logarithmic function of the observed volume and the time lapsing between observations was 0.99. For 7 degrees of freedom ($n-2$, for linear regression) a coefficient of correlation of 0.99 is highly significant.

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A REAPPRAISAL OF THE EFFECTS OF ANTIMICROBIAL THERAPY ON THE COURSE OF APPENDICITIS IN CHILDREN*

WILLIAM R. COLE, M.D., AND HARVEY R. BERNARD, M.D.

St. Louis, Missouri

We have analyzed the hospital records of 965 children who have been operated upon at the St. Louis Children's Hospital because of a diagnosis of acute appendicitis. Despite the evidence which has accumulated indicating the limitations of prophylactic chemotherapy,[1] the question arises repeatedly as to whether or not its effectiveness may not be different among infants and children than it is among adults.

The assessment of the prophylactic effectiveness of the antimicrobials is a difficult problem. Before these substances were discovered, the mortality and morbidity of surgically treated acute appendicitis had already decreased remarkably.[2] In addition, during the time that the antimicrobials have been used, much has been learned and unlearned about the general care of the surgically ill person.

What are the criteria that might provide a fairly objective basis for an evaluation of the prophylactic use of the antimicrobials before an after appendectomies performed on children? The bases for the proposed study are the frequencies of (1) wound infection, (2) intraperitoneal abscess and (3) postoperative death among children during a 5-year period before any of the antimicrobials were used medically 1932 through 1936, and during the 15 years, 1945 through 1959. During the second period the sample consists of 2 parts, children with appendicitis operated upon and not given antimicrobials and those given antimicrobials.†

RESULTS

The data pertinent to the proposed analysis constitute tables 1 through 13, and are self-explanatory. The age seriated frequencies of appendicitis in our groups are similar to those reported by others, and likewise it is also evident that the younger the child with appendicitis, the higher is the frequency of appendiceal perforation. In only 3 cases was the appendix not ruptured among 18 infants under the age of 2 years when they were operated on.

DISCUSSION

The data indicate that the prophylactic administration of chemotherapeutic agents does not affect the wound infection rate in children treated by appendectomy for appendicitis, regardless of the extent of the inflammatory or septic process (tables 4 through 6). The wound infection rates, 1945 through 1959, with and without the administration of antimicrobials, and the wound infection rate, 1932 through 1936, did not differ significantly from one another. Even when the analysis is limited to perforative appendicitis, the postoperative wound infections were as frequent in the chemotherapeutic group as they were when no antimicrobials were given.

There probably is a significant difference between the mortality rate of patients with perforative appendicitis who were treated with antimicrobials as compared to those treated without antimicrobials, favoring the antimicrobial treated group. However, the frequency of death in all groups was so low as to obviate the certainty of the truth of this statement. It is difficult to give the antimicrobial drugs sole credit for this difference because of improvements in many aspects of surgical therapy which have occurred in the past 25 years.

More careful study of the histories of those patients who died makes even more questionable the possibility that significant improvement of mortality statistics resulted from giving the chemotherapeutic agents to children treated by appendectomy for ruptured appendicitis.

Between 1932 and 1936, 2 children died while

* From the Department of Surgery, Washington University School of Medicine and Barnes Hospital, St. Louis, Missouri. This study was supported in part by a grant from the John A. Hartford Foundation, Inc.

† Difficulties related to the microfilming process made it impossible to determine with accuracy the details of chemotherapy between 1936 and 1945. These records, therefore, have not been included in this study.

being operated upon. One died 3 days after a perinephric exploration. A large periappendiceal abscess was found at postmortem. Another died 13 days postoperatively of small bowel obstruction and severe distention. No intra-abdominal

TABLE 1

Number of case studies in each series

Period	Number
1932–1936	213
1945–1959	752
Total	965

TABLE 2

Incidence of appendicitis with perforation in the two series

Period	Total	Perforation	Per Cent Perforation
1945–1959	752	228	30.4
1932–1936	213	66	31.0

TABLE 3

Incidence of removal of normal appendix because of mistaken diagnosis

Period	Total	Normal	Per Cent
1945–1959	752	105	13.9
1932–1936	213	42	19.7

TABLE 4

*Infection rate after appendectomy of nonperforated appendix treated with antibiotics and without antibiotics, 1945–1959**

	No. of Cases	Infections	Per Cent
Antibiotics given	376	20	5.3
No antibiotics given	152	3	2.0
			$P = 0.20$†

* Gives the infection rate after appendectomy for acute appendicitis without perforation, or when a normal appendix was removed in the 1945–1959 series.

† The statistical analyses were all done by the chi-square method.

TABLE 5

*Infection rate after removal of nonperforated appendices, 1932–1936**

	Cases	Infections	Per Cent
No antibiotics	145	5	3.4
			$P = 0.5$

* Gives the infection rate after removal of acutely inflamed or normal appendices in the 1932–1936 series.

TABLE 6

Incidence of infection after operation for perforated appendicitis

Period	Cases	Infections	Per Cent
1945–1959	213	49	23.0
1932–1936	66	13	19.7

TABLE 7

Types and incidence of postoperative infections in the 1945–1959 series

Infection	Number	Per Cent
Wound abscess	36	66
Pelvic abscess	11	22
Right lower quadrant abscess	3	5
Interloop abscess	1	2
Subphrenic abscess	2	3
Cellulitis abdominal wall	1	2
Total	54	

TABLE 8

Types and incidence of postoperative infections in the 1932–1936 series

Infection	Number	Per Cent
Wound abscess	13	65
Pelvic abscess	2	10
Right lower quadrant abscess	0	0
Interloop abscess	3	15
Subphrenic abscess	1	5
Cellulitis abdominal wall	1	5
Total	20	

inflammatory disease existed when he died. Consequently, only 3 children of the 6 who died among the 66 with perforated appendices succumbed postoperatively of intra-abdominal sepsis. Certainly the child who died of intestinal obstruction could not have been saved by antimicrobials. Removing this case alone from the series reduces the probability of the null hypothesis to $P = 0.05$, thereby removing the statistical basis for assigning any benefit to the antimicrobial therapy of perforative appendicitis. Between 1945 and 1959, all children with perforated appendices were given antimicrobials. Out of 227 such cases 5 died; 2 died of sepsis while being prepared for an operation and 3 died postoperatively of intra-abdominal sepsis, one complicated by septicemia.

These data indicate that more benefit can accrue to the child ill of appendicitis by improvements in diagnosis, surgical judgement and technique and general care, than from the indiscriminate use of antimicrobials. In other words, unwarranted confidence has been placed in the utility of the antimicrobials for the treatment of appendiceal intra-abdominal sepsis. This statement does not mean that the antimicrobials cannot and do not play an important part in the immediate and postoperative treatment of perforative appendicitis. However, use of these drugs should be based on good bacteriologic data and largely limited to the treatment of specific infections.

The 5 children during both periods studied were 3 years old or younger, a mortality rate of 5 per cent, whereas the mortality rate of those older than 3 years was 0.8 per cent.* This reflects

* P = less than 0.005.

TABLE 9

*Influence of drains on infection rate in appendicitis with perforation, 1945–1959**

	Cases	Infections	Per Cent
Drains	112	16	14.4
No drains	101	33	33.7
			$P = 0.001$

* Gives the infection rate after removal of perforated appendices when drains were left and when drains were not left in the peritoneal cavity.

TABLE 10

Mortality rate for all types of appendicitis in both series

Period	Cases	Deaths	Per Cent
1945–1959	752	6	0.94
1932–1936	213	6	2.82
			$P = 0.018$

TABLE 11

*Mortality rate after appendectomy without perforation of appendix**

Period	Appendectomies	Deaths	Per Cent
1945–1959	524	1	0.19
1932–1936	147	0	0.00

* Gives the mortality rate after removal of normal or acutely inflamed appendices without perforation in both series. The single death was a patient who had acute gangrenous appendicitis complicating the terminal stages of acute monocytic leukemia.

TABLE 12

*Death rate due to perforated appendicitis**

Period	Perforated Cases	Death	Per Cent
1945–1959	228	6	2.63
1932–1936	66	6	9.1
			$P = 0.022$

* Gives the mortality rate, in both series, following removal of perforated appendices.

TABLE 13

*Incidence of bacteria cultured**

Escherichia sp.	106
Aerobacter aerogenes	11
Staphylococcus albus	8
Staphylococcus aureus	8
Bacillus pyocyaneus	7
Paracolobactrum sp.	3
β-Hemolytic streptococcus	3
Nonhemolytic streptococcus	3
Others	12

* Indicates the bacteria isolated and the frequency with which they were identified at the original operative procedure.

the difficulty in diagnosis of acute appendicitis in very young children. This difficulty in diagnosis probably accounts for the high perforation rate observed among the children under 3 years (84 per cent). Obviously one of the ways that the frequency of perforative appendicitis, with its high morbidity and mortality among very young children, can be reduced is to adopt a more aggressive surgical attitude toward the child with persistent or recurrent abdominal pain.

Only 8 normal appendices were removed from children 3 years of age or younger in our group. This rate of 9 per cent mistaken diagnosis is remarkably low. It is only a little higher than the mortality rate from ruptured appendicitis in this group, and signifies an unwarranted caution that leads to an unwarrantedly high error of diagnostic omission, a perforative rate of 84 per cent. Would it not be better to remove a few more normal appendices, making a few more commissive errors of diagnosis, and thereby reduce the frequency of perforative appendicitis, than to go on making omissive errors at such a rate as to lead to the discovery of 8 perforated appendices for every 10 appendectomies performed upon children younger than 3; especially when the mortality rate attending removal of the nonperforated appendix is 0 in this series of 671 cases (except the case of the child in table 11, who died of acute monocytic leukemia)?

Another surgical problem that has not been solved by the antimicrobials is wound infection. The wound infections that occurred in these children after appendectomy developed in the subcutaneous portion of the wound in 65 per cent of the cases. The question is immediately raised as to whether the surgeon should not treat all contaminated appendectomy wounds by the well known and well documented prophylactically effective technique of delayed primary or secondary wound closure. It might be possible by this simple maneuver to eliminate as much as 65 per cent of the wound infections following appendectomy in children. The actual efficacy of procedure can be determined only after clinical trial.

SUMMARY

The wound infection rates after the removal of the nonperforated appendix in children (1) treated without antimicrobials between the years 1932 and 1936, (2) treated without antimicrobials during years 1945 through 1959 and (3) treated with antimicrobials during the years 1945 through 1959, did not differ significantly from one another. There was no significant difference in the wound infection rate after appendectomy for perforative appendicitis between a group of children treated without antimicrobials between the years 1932 and 1936 and in another group of children treated with antimicrobials from 1945 to 1959. There is a borderline statistically significant difference in the mortality rate between a group of children treated with antimicrobials for perforated appendicitis and a group of children treated without antimicrobials, favoring the group treated with antimicrobials. Virtually no deaths occurred in either group with nonperforative appendicitis. The inordinately high rate of perforation among children under 3 years of age treated for appendicitis combined with the low rate of nonperforated appendices removed from the same group indicates that a more aggressive attitude should be directed toward young children with persistent abdominal pain.

Sixty-five per cent of the wound infections after appendectomy in children might be eliminated by application of the technique of delayed primary or secondary wound closure to all contaminated appendectomy wounds.

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SECONDARY REPAIR OF ARTERIAL INJURIES*

FALLS B. HERSHEY, M.D.

St. Louis, Missouri

The emergency exploration and repair of arterial injuries prevents gangrene, forestalls many other complications and has been highly satisfactory.[1] However, patients occasionally appear in whom arterial injuries were not recognized or were not treated at the time of the original injury. These 8 cases are reported to illustrate a variety of problems and methods of secondary or delayed repair.

METHODS AND MATERIALS

Eight consecutive cases are described which were treated from June 1956 to October 1959. All are injuries of major arteries of the extremities proximal to the knee or elbow; 5 were arteriovenous fistulas and the remaining 3 were false aneurysms. The original injuries had been treated elsewhere. None of the limbs were in peril; however, various complications had resulted from the delay in treatment. The cases of injuries to the femoral artery are detailed in table 1. Table 2 describes the 4 brachial artery injuries.

Diagnosis

The diagnosis was obvious by the time these patients were admitted to the hospital. However, there had been some delay in the diagnosis in 3 cases of femoral arteriovenous (A-V) fistulas because the significance of the bruit and the previous injury was not recognized for some time. Intermittent claudication was treated medically in case 3. Cases 1 and 4 had medical treatment for varicose ulcers resulting from the dilated veins caused by the A-V fistulas. One of these ulcerated legs was definitely warmer than the opposite leg.

In 4 cases, symptoms of A-V fistula did not appear immediately after injury. The bruit was first noted 2 years after the mortar wound in case 1. Films of this thigh showed multiple tiny metallic fragments and apparently one of these slowly eroded between the artery and vein. In case 5, the bruit was first noted a few days after the removal of a cast. In case 7 the bruit appeared after removal of a Steinmann pin. Case 3 developed a bruit weeks after a small knife wound of the thigh had completely healed.

Arteriograms are seldom necessary to make the diagnosis of arterial injury, but are occasionally useful. An arteriogram was made in case 8 when the radial pulse became weak on the affected side and showed a poststenotic aneurysm of the brachial artery which was asymptomatic. In 5 other cases, arteriograms demonstrated the site of the A-V fistula, the degree of proximal dilation of the artery and the distal arterial flow, if any. Arteriograms were contraindicated in a large iliac aneurysm (case 4); arteriograms would have been helpful in case 3 to demonstrate arteriosclerotic stenosis several inches proximal to a small femoral A-V fistula. This might easily have been overlooked. This patient's intermittent claudication was doubtless due to this atheromatous stenosis as well as the traumatic A-V fistula.

Postoperative arteriograms were performed in 5 cases, with results as noted in tables 1 and 2.

Complications Due to Delay in Treatment

Prompt exploration and repair of arterial injuries are necessary to prevent gangrene in some cases. Early operation is also desirable to prevent thrombosis of the outflow tracts which could prevent successful repair later. The cases reported in this paper had conservative treatment elsewhere and their limbs survived, but early operation would have forestalled some of the difficulties encountered.

Two patients experienced mild cardiac decompensation (cases 1 and 7). Case 7 also had attacks of anginal pain and mild cardiac failure which were aggravated by a small brachial A-V fistula. This man apparently has some underlying heart disease and still requires digitalis. Cardiac decompensation in case 1 was relieved completely by repair of a small femoral A-V fistula. Severe cardiac failure can result from large A-V fistulas and can be cured only by operation.

Varicose veins and ulceration of the lower leg

* From the U. S. Veterans Administration Hospital, Homer G. Phillips Hospital and the Department of Surgery, Washington University School of Medicine, St. Louis, Missouri.

TABLE 1

Repair of traumatic aneurysms and A-V fistulas of leg

Case	Age	Arterial Injury	Wounding Agent	Associated Injuries	Date of Injury	Time until Repair	Complications Due to Delay	Preoperative Arteriogram	Date of Operation and Surgeon	Type of Repair	Operation	Follow-up	Pulses	Arteriogram	Functional Result
1	31	Superficial femoral A-V fistula	Mortar shell	Compound fracture	1945	10 yr.	Venous hypertension pulsating varices, edema and ulceration of the leg Cardiomegaly Marked dilation of proximal artery	Fig. 1	July 1955, Hershey	Closure of A-V fistula	Transvenous lateral arteriorrhaphy Ligation superficial femoral vein	1 yr.	Normal	Normal (fig. 1, 8/23/55)	Normal leg and heart Arterial dilation reversed Died of leukemia
2	30	External iliac False aneurysm	0.32 caliber pistol	Injury to femoral nerve Perforation of iliac vein Large hematoma	April 1958	3 mo.	Poor pulses in foot Thrombosis of iliac vein, persistent lymphedema of leg 20- x 6-cm. mass of ectopic bone arose in muscle and hematoma	False aneurysm	July 1958, Hershey and Oliver	Prosthesis	7-cm. DeBakey prosthesis from external iliac to superficial femoral artery (fig. 2) Ligate profunda artery, repair iliac vein Resect ectopic bone and false aneurysm	1½ yr.	Normal		Good result of arterial reconstruction Persistent lymphedema, recurrent dermatitis and lymphangitis relieved by pneumatic boot Slow recovery from femoral nerve injury and quadriceps weakness
3	32	Superficial femoral A-V fistula	Stab wound	None	1949	7 yr.	2-3 yr. intermittent claudication Proximal artery dilated up to 14-mm. diameter and fragile Edema of foot	None	No., 1956, Avery and Hershey	Vein graft	End-to-end anastomosis after resected small A-V fistula Vein graft after resect intramural hematoma at site of clamp (fig. 3)	3 yr.	Normal	Normal (fig. 3)	Relief of intermittent claudication Relief of edema of foot Vein graft same size as artery No stricture of anastomosis
4	62	Superficial femoral A-V fistula	Pistol	Fracture of femur	1932	20 yr.	Varicose ulcer		USMH, Kirkwood, Mo. 1952	No repair	Ligation of superficial femoral artery; repair of vein	8 yr.	Normal	None	Cured A-V fistula and varicose ulcers; developed aneurysm proximal to ligature
		True aneurysm common femoral and iliac artery (fig. 4)				8 yr.	Aneurysm formation	None	July, 1959, Hershey and Meirs	Prosthesis	Resection of iliac and femoral aneurysm Bifurcation prosthesis sutured to end of profunda and superficial femoral artery	3 mo.	Normal	None	Postoperative lymphocele in groin incision became persistent sinus
									Nov. 1959, Hershey and Adams		Pedicle flaps closure of foreign body sinus	1 mo.	Normal	None	Sinus recurred
									Jan. 1960, Hershey	Excision prosthesis	Ligation external iliac artery; ligation deep femoral artery; lateral arteriorrhaphy superficial femoral artery				Postoperative gangrene required high thigh amputation

TABLE 2

Repair of traumatic aneurysms and A-V fistulas of arm

Case	Age	Arterial Injury	Wounding Agent	Associated Injuries	Date of Injury	Time Until Repair	Complications Due to Delay	Preoperative Arteriogram	Date of Operation	Type of Repair	Operation	Follow-up	Pulse	Arteriogram	Functional Result
5	22	Brachial A-V fistula	0.22 caliber pistol	Supracondylar fracture	April 1950	2 mo.	Expanding false aneurysm 3-cm. diameter Pain and prolongation of disability	Yes	June 1956	End-to-end anastomosis	Excision of fistula; debride 1 cm. of artery each end; end-to-end anastomosis	2 mo.	Normal	Normal 2 mo. postoperative	Good arterial repair Lost to follow up
6	35	Brachial A-V fistula	Pistol	Partial median nerve injury	June 1956	8 days	False aneurysm 8-cm. diameter, absent radial pulse	Fig. 5	June 1956, Gaffney and Hershey	End-to-end anastomosis	Ligation of veins; excision of aneurysm	2 mo.	Normal	Normal 2 mo. postoperative	Good arterial repair Residual median nerve defect; lost to follow up
7	43	Brachial A-V fistula	Steinmann pin	Supracondylar fracture due to fall	1944	15 yr.	Loss of use of arm, pain and disability, contracture of elbow Proximal artery dilated 2 × normal Mild cardiac failure and anginal pain	None	Sept. 1959 Adams and Hershey	End-to-end anastomosis	Ligation of veins; excision of aneurysms Ligation of veins; end-to-end suture of artery	8 mo.	Normal	None	Good arterial repair Heart improved but still needs digitalis; arm free of pain and contracture improving with use of arm
8	47	Brachial transection	Pistol	Hemothorax median nerve palsy	April 1956 (primary repair followed by weak pulses)	10 mo.	Poststenotic aneurysm at site of anastomosis Proximal and distal arteriosclerosis	August 1956	Feb. 1957, Gaffney and Hershey	Vein graft	Excise aneurysm and proximal arteriosclerosis up to profunda brachii artery Diffuse narrowing distally	2 yr.	Fair	2 mo. postoperative occlusion of graft	Graft occluded due to proximal and distal arteriosclerosis; good function for manual labor; slight residual median nerve injury

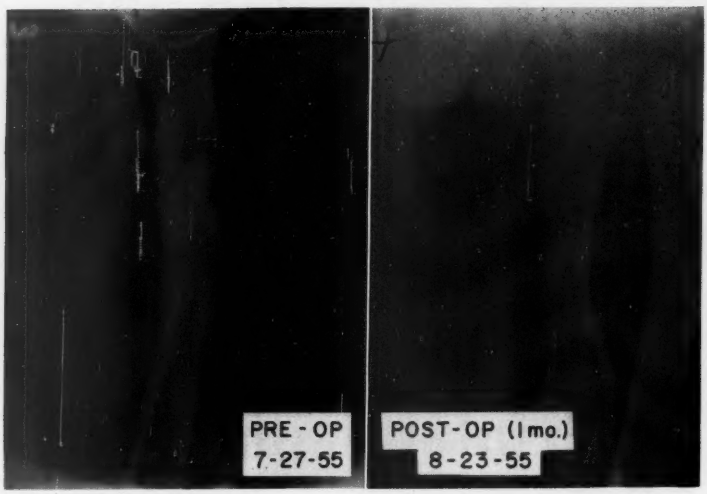

FIG. 1. Case 1, superficial femoral arteriovenous fistula preoperative and postoperative arteriograms

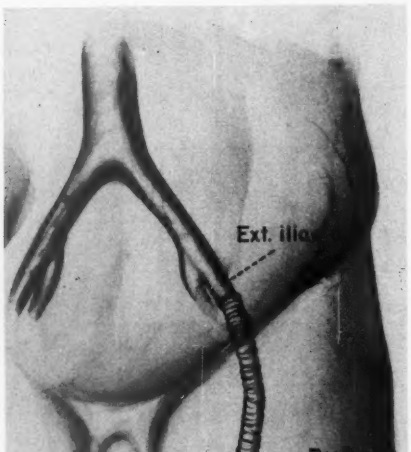

FIG. 2. Case 2, artist's sketch of prosthesis replacing false aneurysm of iliac and upper femoral artery

are common complications of femoral A-V fistula, as a result of the venous hypertension (cases 1 and 4). Closure of the arterial communication cured these ulcers. The varicosities did not need surgical treatment thereafter.

Untreated injuries of the accompanying veins can also lead to serious complications. Massive lymphedema of the leg from iliac vein thrombosis was very troublesome before and after delayed repair of the external iliac artery (fig. 2, case 2). The edema was due partly to iliac vein thrombosis and obstruction at the old perforation of the vein. This patient had recurrent infections and ulcerations until the edema was controlled by pneumatic leggings. Repair of the vein may have been feasible at an early operation, but was unsuccessful at the secondary repair.

The local pathology in the region of an old arterial injury is frequently more troublesome to the surgeon than the bleeding and hematomas and other findings at early operation. One case also had a bony, hard, calcified hematoma of the lower abdominal wall, groin and upper thigh. This mass had to be excised in order to approach the artery. The A-V fistulas are surrounded by large venous collaterals which must be patiently dissected and ligated. The wall of the false aneurysms at the site of the arterial perforation is formed from the surrounding soft tissue. There is

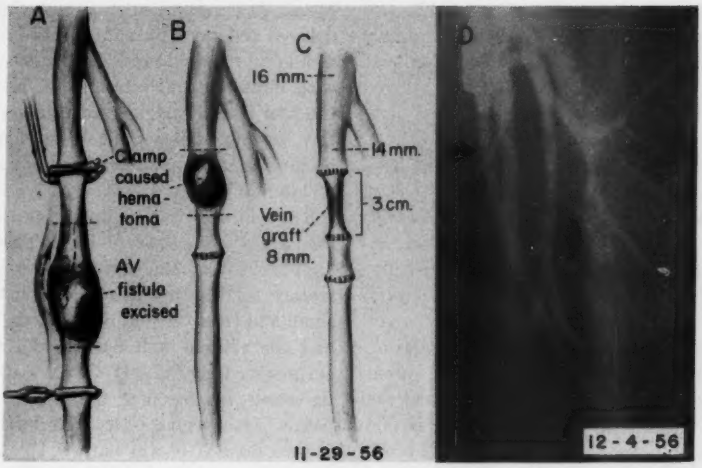

FIG. 3. Case 3. *A*, artist's sketch of superficial femoral A-V fistula. *B*, end-to-end anastomosis after excision of fistula. Intramural hematoma developed at site of Blalock clamp. *C*, sketch of vein graft after excision of hematoma showing size discrepancies. *D*, postoperative arteriogram. *Arrows* show sites of anastomosis.

no easy plane of dissection around such aneurysms. Proximal and distal artery and vein and nerves may be incorporated in the wall of false aneurysms for considerable distances.

Pathologic changes in the damaged artery may be very striking. Debridement may be as extentive as in primary repair. The artery proximal to an A-V fistula may dilate to considerable size and become fragile (fig. 1, case 1). In case 3 the fragile and dilated artery was crushed by a Blalock clamp and developed a hematoma in its wall (fig. 3*A* and *B*, case 3). This section of the artery was replaced with a vein graft (fig. 3*C*). Serrifine bulldog clamps are preferable to crushing types of arterial clamps.

Pathologic changes in the artery are not reversed by ligation of A-V fistulas. Dilation of the artery may progress proximal to the ligature until a true aneurysm develops (case 4). This case developed a true aneurysm of the common femoral and iliac artery 8 years after ligation of the superficial femoral artery for an A-V fistula. At our operation the arterial collateral circulation proximal to the ligature flowed through greatly dilated vessels. The external iliac artery measured 22 mm. in diameter proximal to the aneurysm. The common iliac and hypogastric arteries on affected side were even larger than this. The profunda femoris measured 11 mm. in diameter. The superficial femoral artery distal to the ligation was twice the normal diameter (9 mm.). The size of these vessels at the time of the ligation is unknown, but it is clear that treatment by ligation did not restore normal physiology or reverse the dilation of the artery. Similar cases have been reported.[3] Repair of the fistula instead of ligation permits the proximal dilation to return to normal (case 1, fig. 1).

Two cases had arteriosclerotic narrowing proximal to an old arterial injury, and it is not clear whether the arteriosclerosis preceded or was aggravated by the injury. One of these cases had diffuse narrowing of the brachial artery up to the profunda brachii. The other case had intermittent claudication of the leg and absent pedal pulses due to a femoral A-V fistula and a proximal atherosclerotic plaque. Pulses were restored and the intermittent claudication was relieved by resection of both lesions with a vein graft to restore arterial continuity (case 3).

Treatment and Results

The treatment and results are summarized in tables 1 and 2. Repair was successful in all but 2 cases and both of the failures had previous operations elsewhere. Earlier repair might have forestalled some of these difficulties and would have shortened the period of disability. Only one case

had no symptoms (case 8), and most of them had gone on for many years in spite of serious symptoms and disability. Delay for development of collateral circulation or for preliminary sympathectomy is unnecessary because arterial continuity will be restored.

The cardinal principles of arterial repair have been verified by experience. Long incisions are placed so that proximal and distal control of the normal artery and vein is obtained before approaching the aneurysm or fistulas. Serrifine arterial clamps and 4-0 and 5-0 arterial sutures must be available.

Frequently the fistula can be located and occluded with the pressure of a finger tip. The proximal and distal occluding clamps are closed and the artery is traced down to the fistula. It may be simpler and easier to approach a small fistula by opening the vein wall opposite to the fistula.

False aneurysms are densely adherent and sometimes dealt with easily by being opened if dissection around them proves difficult. Proximal and distal occlusion of the main vessels is essential before opening the sac. Troublesome oozing from collateral may occur inside the aneurysm and these collaterals are dealt with individually after the sac is opened.

Continuity of the artery is always restored. The older treatment, quadruple ligation of the proximal and distal artery and vein, may be followed by crippling intermittent claudication or delayed aneurysm formation. The brachial artery should be repaired even though it can be ligated with impunity and intermittent claudication of the arm is exceedingly rare. Successful repair of the brachial artery will make arteriosclerotic occlusions and emboli less disabling if they occur in later life.

The simplest method to restore continuity of the artery is lateral repair. This is seldom applicable, but the technique is highly satisfactory for the rare case in which the fistula is small and transverse in position, the artery large, and the arterial wall normal and able to hold sutures securely (case 1). Occasionally the easiest approach is to open the vein opposite the fistula. Transvenous lateral arteriorrhaphy should not be done if it will narrow the lumen of the artery; therefore, it is rarely used.

End-to-end anastomosis was performed in 4 cases after resection of small traumatic aneurysms or fistulas. This method is usually applicable with small lesions in the brachial artery (cases 5, 6 and 7). Some tension on the arterial anastomosis is normal, but excessive tension leads to spasm, thrombosis or disruption. It is unwise to divide collateral branches or to flex joints in order to permit end-to-end anastomosis. When end-to-end anastomosis is not feasible, vein grafts or prostheses are used.

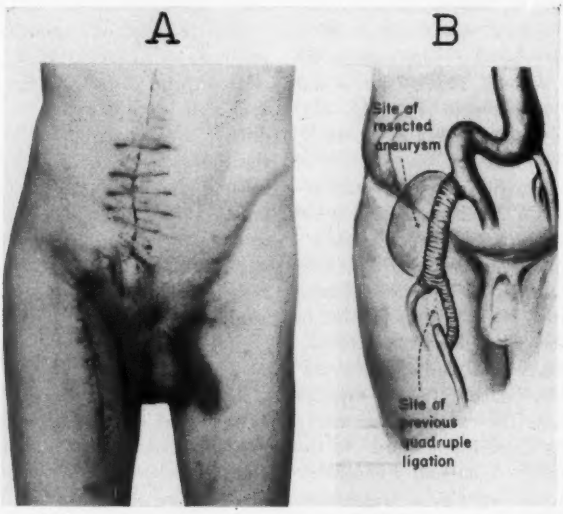

FIG. 4. Case 4, large iliofemoral aneurysm. *A*, photograph 18 days postoperatively showing incision. Apparently healed. *B*, sketch of excised aneurysm and bifurcation prosthesis used to replace it.

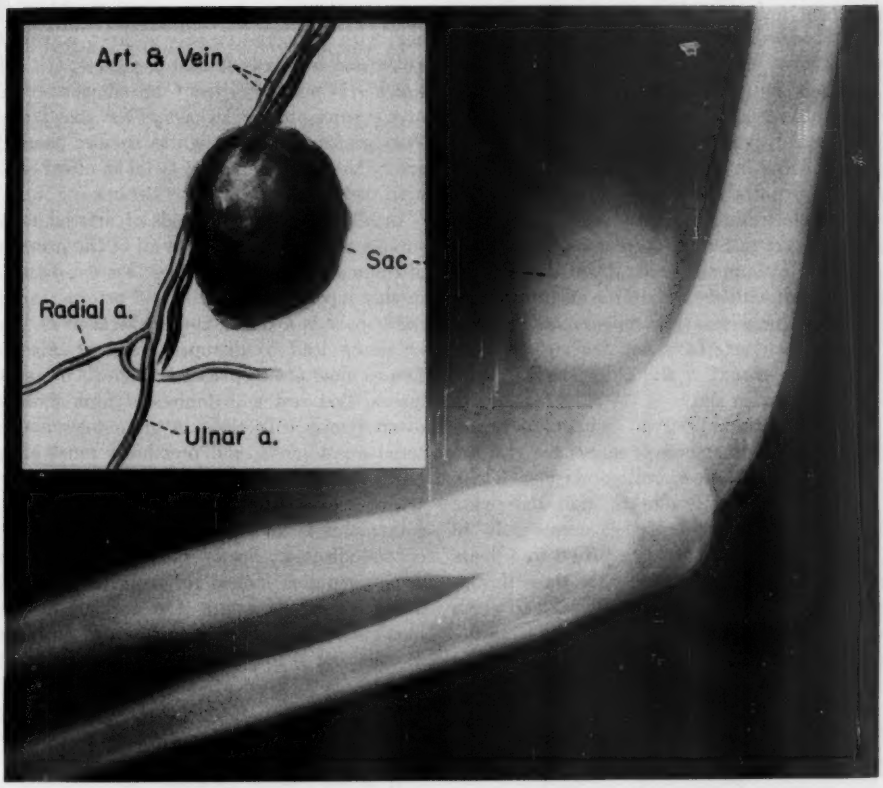

FIG. 5. Case 6, large traumatic aneurysm and A-V fistula of brachial artery

Arterial prostheses are necessary for the replacement of large arteries because vein grafts will form aneurysms in these locations. All forms of external support thus far applied in the experimental laboratory have been unsuccessful. Prostheses of the DeBakey Dacron type were used in 2 cases for iliac artery replacement as illustrated in figures 2 and 4. The bifurcation prosthesis (fig. 4) measured 22 mm. in proximal diameter and was clearly the only feasible method to restore continuity after resection of the large iliac aneurysm. The incisions apparently healed (fig. 4). Three weeks postoperatively, when the patient was permitted to walk, lymph and fluid collected about the prosthesis and a sinus later developed in the groin. A flap of sartorius muscle and skin closed the sinus temporarily, but the prosthesis was finally removed 3 months after the original operation. Gangrene developed and a high thigh amputation was required. This was the only amputation in this series. The other prosthesis is still open 1½ years postoperatively.

Small diameter prostheses are quickly occluded by the thick fibrin pseudointimal lining. Experimental results with prostheses less than 4 mm. in diameter are highly unsatisfactory and clinical trial seems unwarranted, although the critical size is not clearly established.

Autogenous vein grafts are highly satisfactory to bridge defects in peripheral arteries distal to the iliac or subclavian arteries. Cases 3 and 8 are examples of the use of vein grafts during secondary repairs. Our 12 cases with vein grafts for repair of acute arterial injuries have convinced us that autogenous vein grafts are superior to arterial homografts for both primary and secondary repairs, probably because they are the patient's own living tissue and have a smooth

endothelial lining. Vein grafts have not been widely used because of the ready availability of homografts or prostheses and because of reports of dilation and aneurysms developing in vein grafts replacing large arteries in the experimental laboratory.[7] Experience has proved that dilation does not occur in small arteries. Review of the published reports shows that dilation of mild degrees, which was not progressive, occurs in some vein grafts but is uncommon.[5, 6] Various maneuvers to support or reinforce the wall of the vein graft with the wall of the aneurysm, and so forth, are unnecessary in replacement of small arteries. Aneurysms have not developed in any of our cases thus far, the oldest having been repaired 6½ years ago.[2]

Subsequent thrombosis of vein grafts is frequent when long segments of saphenous vein are used to bypass arteriosclerotic occlusions. These failures are probably due to the underlying arteriosclerosis. Thrombosis has occurred in 40 per cent of the Korean vein grafts 3 to 4 years after the repair.[4] We suspect that these thromboses have arisen in the part of the artery which sustained invisible microscopic damage from the cavitation effects of the missiles. Therefore, it is our present policy to resect 1 to 2 cm. of grossly normal artery in recent gunshot wounds. In secondary repairs we resect only the grossly damaged artery.

In our series of vein grafts only one occlusion has occurred thus far (case 8). This occlusion was due to proximal arteriosclerosis. Further clinical experience and longer follow-up are needed to test their value, but vein grafts appear to be the best long term replacement for small vessels at the present time.

The technique of vein grafting is easily mastered, but it is more delicate and meticulous than suture of arterial homografts or prostheses. The technique is the same as described for acute arterial injuries.[1, 2] The vein that accompanies the injured artery is repaired if it appears practicable, and the vein graft is taken from the uninjured extremity. Certain precautions are necessary because the vein wall is easily injured. It is not elastic and therefore the vein graft must be cut to the correct length. Drying is prevented and viability insured by removing the vein only when the operative site is ready for anastomosis. Vein walls are thin and will collapse and wrinkle unless held with triangulating stay sutures. Narrowing at the anastomoses will lead to poststenotic dilation and is not permitted. Continuous over-and-over sutures prevent leakage at the anastomosis. Vein grafts that are slightly smaller than the artery have been observed to be identical in size with the artery in later arteriograms (fig. 3).

In all the various methods of arterial repair, success requires attention to all of the principles of traumatic surgery, but these are not discussed in this report. In the repair of arterial injuries dead space is avoided, since collections of blood or serum lead to disruption and/or infection. Drains must not be placed near grafts or anastomoses. Bed rest will diminish lymph flow and avoid lymph collections in groin incisions. Arterial anastomoses and prostheses must always be covered by living tissue. If there has been extensive loss of soft tissue, it may be necessary to rotate muscle or skin flaps. Anticoagulants are contraindicated. Postoperative arterial insufficiency requires immediate reoperation because paravertebral blocks are of no value in restoring blood flow through the main channel, and dilation of collateral is frequently insufficient to prevent catastrophe.

SUMMARY

1. When trained personnel and facilities are available, primary repair of arterial injuries avoids some of the early and the delayed complications.

2. Arterial continuity must always be restored. The principles and techniques are similar to the repair of acute injuries, except that grossly normal artery need not be debrided.

3. End-to-end anastomosis is preferable when it can be accomplished without undue tension on the suture line or without sacrifice of collateral branches.

4. Prostheses are necessary for repair of defects in large arteries such as the iliac.

5. Vein grafts are preferable for restoration of arterial continuity distal to the clavicle and groin.

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THE THERAPEUTIC EFFICACY OF ANTICOAGULANT DRUGS FOR PULMONARY EMBOLI AND INFARCTS*

PAUL E. STOHR, M.D., IRWIN K. ROSENBERG, M.D., AND HARVEY R. BUTCHER, JR., M.D.

St. Louis, Missouri

This study was undertaken to evaluate the worth of anticoagulant drugs as they are used in the Barnes Hospital for the treatment of pulmonary emboli and infarcts.

MATERIAL

The case records were studied of all persons who had had pulmonary emboli between January 1, 1942, and January 1, 1953. The sample consists of 302 cases, in 230 of which the diagnosis was made solely from roentgenographic and physical signs; in 60 the diagnosis was made either at necropsy only or from roentgenographic and physical signs immediately before death. Twelve others were not included in the principal treatment groups for various reasons (see group C, table 1). The methods of treatment are summarized in table 1.

Treatment was considered successful when no further embolization occurred and the patient did not die with a pulmonary embolus. Treatment was regarded as a failure if a nonfatal pulmonary embolus or infarct occurred during treatment or soon after its discontinuance. Therapy also was considered a failure if it was discontinued because of a complication of treatment, or if the patient died with a pulmonary embolus during the treatment or soon after its discontinuance (table 2).

RESULTS

The annual distribution of patients with pulmonary emboli and infarcts, the incidence of thrombophlebitis and the number of hospital admissions are shown in tables 3 and 4 (figs. 1 and 2). Two hundred thirty patients were treated by bed rest, elevation of the legs and elastic supports if signs of thrombophlebitis were present and analgesics if pleuritic pain existed. Of these 230 patients, 118 also received anticoagulant drugs (treatment method A) whereas the remaining 112 did not (treatment B). The success rate of treatment when anticoagulant drugs were administered did not differ significantly from that of treatment which did not include anticoagulation (tables 5 and 6).

Tests of the homogeneity of the distribution

TABLE 1

Pulmonary emboli and infarcts: methods of treatment

Method	No. of Patients	Method of Treatment
A	118	Bishydroxycoumarin or related drugs after receiving heparin initially. Treatment included bed rest, elevation of the legs and elastic supports when thrombophlebitis existed
B	112	Bed rest, elevation of the legs and elastic supports when signs of thrombophlebitis existed; by narcotic drugs to control pleuritic pain; and by oxygen inhalation if dyspnea or cyanosis developed
Group C	72*	

* Not included in the principal treatment groups. Sixty had pulmonary emboli but were not treated because the embolus was discovered only at necropsy or was diagnosed as the cause of sudden death. The diagnosis was doubtful in 6 others, had been made 6 or more weeks before hospitalization in 3, and was not confirmed at necropsy in 1 (only the latter patient received anticoagulant drugs). Of the 2 remaining, 1 left the hospital within 24 hours against advice and the other had a pulmonary embolus while on anticoagulant drugs for thrombophlebitis which was treated by venous ligation.

* From the Department of Surgery, Washington University School of Medicine and Barnes Hospital, St. Louis, Missouri. This study was supported in part by a grant, H-2569(C4), from the National Heart Institute of the National Institutes of Health, United States Public Health Service.

TABLE 2

Nonfatal pulmonary embolus classification of therapeutic results

I. Successful therapy (S): Patients diagnosed as ill of pulmonary embolization or infarction whose symptoms and signs subsided without further complication

II. Unsuccessful therapy (F): Patients diagnosed as ill of pulmonary embolization who developed any of the following complications:
- A. Death diagnosed as caused by another embolus or at least in part by the initial one more than 24 hours after diagnosis and found postmortem if an autopsy was performed
- B. Recurrence of pulmonary symptoms and signs sufficient to have been diagnosed as resulting from more nonfatal pulmonary emboli
- C. Recurrent pulmonary emboli occurring soon after treatment was stopped
- D. Hemorrhagic diathesis during treatment

TABLE 3

Year of diagnosis and treatment of 302 persons ill of pulmonary emboli and infarction

Year of Diagnosis	Treatment Method		Group C*	Total	No. Dying of All Causes	No. of Patients with Thrombophlebitis	No. of Hospital Admissions
	A*	B*					
1942	0	7	7	14	7	19	12,051
1943	0	9	7	16	11	20	11,462
1944	1	11	1	13	6	51	14,578
1945	1	14	2	17	5	34	17,663
1946	4	12	4	20	10	61	19,455
1947	9	8	4	21	7	66	21,004
1948	23	11	12	46	19	96	21,765
1949	20	13	8	41	16	106	21,761
1950	29	15	10	54	19	120	22,385
1951	14	8	6	28	7	97	22,572
1952	17	4	11	32	13	49	23,136
Total...	118	112	72	302	120		

* Number dying in the hospital: A, 20; B, 39; and C, 61.

of patients in the 2 treatment groups by age, sex and associated illnesses showed them to be comparable except for a higher incidence of thrombophlebitis among the patients treated by method A than among those treated by method B (tables 7 to 9). However, methods A and B were equally effective in the treatment of pulmonary embolus or infarct as it occurred among patients with and among those without thrombophlebitis (table 12). Treatment periods for the 2 groups differed, since anticoagulant drugs were used infrequently before 1947; however, separate analysis of the results among the patients treated during the years 1947 through 1951 also failed to show any benefit from the anticoagulant drugs (table 6). The frequency of various signs and symptoms of pulmonary infarction among the 2 treated groups of patients was the same (table 10).

Associated primary illnesses were divided arbitrarily into serious and minor illnesses (table 11) and, as might be expected, failure of treatment was significantly more frequent in the former groups. The results of methods A and B did not differ, however, within any of the disease groups (tables 11 and 12).

TABLE 4

*The incidence of thromboembolic phenomena in the Barnes Hospital**

Year of Diagnosis	Thrombophlebitis	No. of Patients with Pulmonary Emboli	No. of Deaths among Patients with Pulmonary Emboli
1942	16	12	6
1943	18	14	10
1944	34	9	4
1945	19	10	3
1946	32	11	5
1947	31	10	3
1948	44	21	9
1949	48	19	7
1950	54	25	8
1951	42	12	3
1952	21	14	6
Mean number per 10,000 hospital patients per year	32.6 ±13.2†	13.4 ±5.3	5.8 ±2.3
95 percentile variance	32.6 ±25	13.4 ±10.1	5.8 +4.4

* Per 10,000 hospital patients.

† Standard deviation.

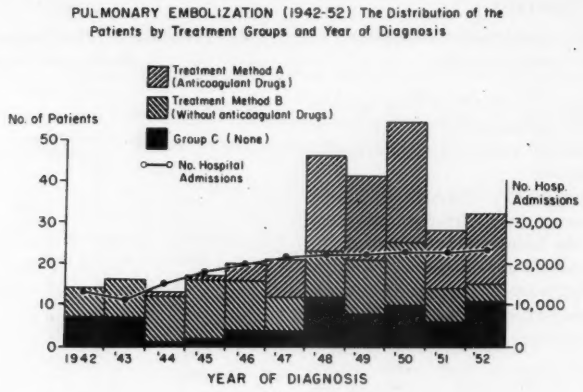

FIG. 1

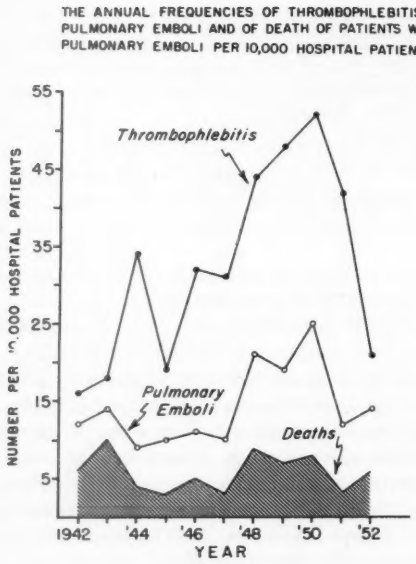

FIG. 2

TABLE 5

The results of treatment nonfatal pulmonary emboli (1942 to 1952)

Treatment Method	No. of Patients	Results of Treatment		Chi Square	*P* (A = B)
		S*	F*		
A	118	66 (56%)	52		
B	112	67 (60%)	45	0.36	0.57
Total....	230	133 (58%)	97		

* S, successful; F, unsuccessful.

TABLE 6

The results by year of treatment

Time of Diagnosis and Treatment	Treatment A			Treatment B		
	Result		No. of Patients	Result		No. of Patients
	S	F		S	F	
1942			0	5	2	7
1943			0	7 (2)*	2 (2)	9
1944	1	0	1	6	5 (5)	11
1945	1	0	1	10	4 (3)	14
1946	2	2 (1)	4	6	6 (5)	12
1947	4	5 (3)	9	5	3 (3)	8
1948	11	12 (4)	23	8 (1)	3 (3)	11
1949	12 (1)	8 (3)	20	5	8 (5)	13
1950	15	14 (4)	29	6	9 (7)	15
1951	9	5 (1)	14	4	4 (2)	8
1952	11	6 (3)	17	2	2 (1)	4
Total...	66 (1)	52 (19)	118	67 (3)	45 (36)	112

Therapy A was no better than B (table 5). The results of treatments A and B in the years when many of the patients were treated by both methods (1947 through 1951) likewise did not differ from one another (chi square = 0.101; P = 0.75).

* Numbers in parentheses indicate the number of patients dying of all causes.

ANALYSIS OF THE FAILURES OF THERAPY

The mortality from pulmonary emboli and infarcts was similar in the 2 groups (table 13). However, total mortality was greater among patients treated by method B (table 14). The higher mortality rate in the latter group was attributable to the greater mortality from their

TABLE 7

Homogeneity of the age distributions of patients treated for nonfatal pulmonary emboli with (A) and without (B) anticoagulant drugs

Age	Treatment Method	
	A	B
yr.		
20	2	2
21–30	5	8
31–40	17	9
41–50	28	23
51–60	25	36
61–70	29	22
71–80	10	11
81+	2	1
Total	118	112

The age distribution of patients treated successfully did not differ from that of the ones treated unsuccessfully (chi square = 5.56; $P_7 = 0.6$).

TABLE 8

The homogeneity of the sex distributions of patients treated for nonfatal pulmonary emboli with (A) and without (B) anticoagulant drugs

Treatment	No. of Patients	No. of Men	No. of Women	Chi Square	*P*
Method					
A	118	73	45		
B	112	74	38	0.44	0.5
Total	230	147	83		
Results					
Success	133	87	46		
Failure	97	60	37	0.31	0.6
Total	230	147	83		

primary illness (table 15). Examination of the relationship of the prothrombin times to the causes of treatment failure did not show improved results among those patients having 75 per cent or more of their prothrombin time determinations below 30 per cent of normal (tables 16 to 18).

DISCUSSION

The analysis of the data presented failed to show the merit of the anticoagulant regimen used

TABLE 9

The distribution by associated disease states and treatment method of patients thought to have nonfatal pulmonary emboli

Primary Illness	No. of Patients (230)	Treatment Method		Chi Square	*P* (1 = 2)
		A (118)	B (112)		
Heart disease					
Present	100	48	52		
Absent	130	70	60	0.77	0.4
Malignant neoplasm					
Present	26	12	14		
Absent	204	106	98	0.31	0.6
Thrombophlebitis					
Present	48	35	13		
Absent	182	83	99	11.2	<0.001
Operation for non-neoplastic disease					
Yes	35	15	20		
No	195	103	92	1.18	0.3
Miscellaneous illness					
Present	21	8	13		
Absent	209	110	99	1.73	0.2

in the Barnes Hospital (1942 to 1952) to treat patients having pulmonary emboli and infarcts. The results of treatment without anticoagulant drugs were no poorer than were the results of treatment which included their use. The patients comprising the treatment groups, although not randomly selected, had similar age and sex distributions, the same frequencies of the symptoms and signs of pulmonary infarct, and of associated heart disease, malignant neoplasm and postoperative states. The 2 treatment groups apparently differed in 2 ways. They were not treated with equal frequency during the years of the study, and the group of patients for whom anticoagulant drugs were used had a significantly higher frequency of associated thrombophlebitis. The results among the patients receiving anticoagulants were favored, since the treatment of pulmonary emboli when associated with primary thrombophlebitis was more successful than when associated with cardiac disease or neoplasm (table 12). The large number of patients treated by method A in the years 1948 to 1951 corresponded to the period of greatest incidence of thrombophlebitis (figs. 2 and 3). Despite the influence of the high frequency of primary

TABLE 10

The frequencies of the symptoms and signs of pulmonary infarction among persons thought to have nonfatal pulmonary emboli and treated by methods A and B

	Results of Method A (No. of Patients)			Results of Method B (No. of Patients)			Comparison of Groups A and B	
	S	F	Total	S	F	Total	Chi square	*P*
Symptom or sign present	66	52	118	67	45	112		
Pleurisy	59	41	100	62	31	93	0.124	0.72
Hemoptysis	40	30	70	37	32	69	0.125	0.72
Pleural effusion	49	42	91	43	37	80	0.975	0.34
Roentgenographic changes	38	36	74	41	22	63	0.995	0.33

TABLE 11

The results of treatment for nonfatal pulmonary embolization

Treatment Method	No. of Patients	Results of Treatment		Chi Square	*P* (A = B)
		S	F		
1. Patients with serious primary illnesses (malignant neoplasms, heart disease, major emergency operations)					
A	71	33	38		
B	80	41	39	0.14	0.7
Total	151	74	77		
2. Patients having associated thrombophlebitis, elective operations or minor primary illnesses					
A	47	33	14		
B	32	26	6	1.23	0.27
Total	79	59	20		

Comparing group 1 with group 2 (total results), chi square = 14.06; $P = <0.001$.

thrombophlebitis upon the results of method A, they could not be shown to be significantly better than the results of method B.

Another observation suggesting that anticoagulant drugs are of little therapeutic value among patients with pulmonary emboli was the apparent lack of a relationship between plasma prothrombin levels and the success or failure of treatment (table 17).

TABLE 12

The relationship of primary illnesses to the results of treatment

Primary Illness and Treatment Method	No. of Patients	Results of Treatment		Chi Square	*P*
		S	F		
1. Heart disease					
A	48	20	28		
B	52	30	22	2.56	0.12
Total	100	50	50		
2. Malignant neoplasm					
A	12	6	6		
B	14	4	10	1.25	0.27
Total	26*	10	16		
3. Thrombophlebitis					
A	35	23	12		
B	13	10	3	0.54	0.47
Total	48	33	15		
4. Operation for nonneoplastic diseases					
A	15	12	3		
B	20	15	5	0.12	0.73
Total	35	27	8		
5. Miscellaneous					
A	8	5	3		
B	13	8	5	0.001	0.96
Total	21	13	8		

* Of these 26, 7 were not operated on because of the advanced stage of their cancer; 6 were therapeutic failures, 5 were treated by method B, and 4 were failures.

TABLE 13

An analysis of the failures of therapy

Treatment Method	No. of Treatment Failures	No. of Patients	Number Fatal	Time of Recurrent Pulmonary Emboli		Hemorrhage*
				During therapy	After cessation of drug therapy	
A	52	48	13	36	12	4
B	45	45	16			
Total...	97	93	29†			

* Intra-abdominal, genitourinary, pulmonary and subcutaneous bleeding.

† The mortality from fatal emboli among persons treated by the two methods did not differ (chi square = 0.78; $P = 0.4$). The mortality from all causes was greater among patients in the treatment B group (table 14).

TABLE 14

Mortality from all causes

Treatment Method	No. of Patients	No. of Patients Dying	No. of Patients Surviving	Chi Square	P (A = B)
A....	118	20	98		
B....	112	39	73	9.64	0.002
Total....	230	59	171		

Patients treated by method A died in the hospital significantly less often than did those treated by method B (table 14). This difference was attributable to the more serious underlying illness of the patients in group B (or a higher incidence of the less fatal pulmonary emboli incident to thrombophlebitis among patients treated by method A).

The only valid conclusion from this study is that anticoagulant drug therapy as used in the Barnes Hospital did not benefit the patients who received it as treatment for pulmonary emboli and infarcts. The currently held concepts—(1) that plasma prothrombin time values of less than 30 per cent or normal assure the best results and (2) that fatal pulmonary emboli rarely accompany anticoagulant therapy instituted for pulmonary emboli—are not supported by this study.

TABLE 15

Mortality from all causes (breakdown of table 14)

Treatment Method	Results of Treatment	No. of Patients Dying in the Hospital	Cause of Death*		
			(1) Recurrent embolus	(2) Recurrent pulmonary embolus and primary disease†	(3) Primary disease
A {S‡.....	66	1	0	0	1
A {F.....	52	19	13	4	2
Total....	118	20	13	4	3
B {S.....	67	2	0	0	2
B {F.....	45	37	16	10	11
Total....	112	39	16	10	13
Total.....	230	59	29	14	16

	Chi square	P
* Comparing the incidences (A with B) of:		
Fatal embolus (1).....	0.78	0.4
Death from primary illness (3).....	7.29	0.009
Death from (1) and (2)† combined.....	2.18	0.15

† Impossible to ascertain part played by possible recurrent embolus in person's death.

‡ S = successful; F = failure.

TABLE 16

The distribution of the prothrombin time values just before hemorrhage or recurrent embolization among the patients treated by anticoagulation

Prothrombin Time, % of Normal	No. of Failures	Cause of Treatment Failure	
		Hemorrhage	Recurrent pulmonary embolus during treatment
		no. of patients	
0–10	4		4
11–20	7	1	6
21–30	17	2	15
31–40	7	1	6
Total.....	35*	4	31

* Seventeen others had pulmonary emboli within 1 month after anticoagulant drugs were stopped.

TABLE 17

The recorded prothrombin time determinations compared with the results of treatment method A

Treatment†	No. of Patients	No. of Patients with Prothrombin Times above 30% of Normal in		Prothrombin Time Determinations		
		25% or less of recorded determinations	More than 25% of recorded determinations	None recorded	No. recorded*	No. above 30% of normal
S	66	25	38 (60%)	3	858	280 (33%)
F	52	27	24 (47%)	1	718	250 (35%)
Total.....	118	52	62‡	4	1576	530 (34%)

* Only those performed more than 48 hours after institution of Dicumarol therapy are included.

† S = successful; F = unsuccessful.

‡ The results among patients having 75% of their prothrombin time determinations below 30% of normal were no better than the results among the patients having less than 75% of their prothrombin time values below 30% of normal (chi square = 2.00; $P = 0.17$).

TABLE 18

Prothrombin time data of patients treated by method A

Year	Results of Treatment	No. of Patients	No. of Patients with Prothrombin Times above 30% of Normal in		Total No. of Prothrombin Time Determinations (48 or more hours after beginning treatment)	No. above 30% of Normal
			25% or less of recorded determinations	More than 25% of recorded determinations		
1944	S*	1	0	1	10	9
	F*	0	0	0	0	0
1945	S	1	0	1	5	5
	F	0	0	0	0	0
1946	S	2	0	2	28	17
	F	2	1	1	8	2
1947	S	4	2	2	26	11
	F	5	1	4	72	40
1948	S	11	3	8	158	66
	F	12	8	4	205	53
1949	S	12	4	8	187	58
	F	8	3	5	67	24
1950	S	15†	5	7	143	46
	F	14‡	7	6	172	72
1951	S	9	6	3	169	32
	F	5	3	2	86	28
1952	S	11	5	6	132	36
	F	6	4	2	108	31
Total.....	S	66	25	38	858	280
	F	52	27	24	718	250

* S, successful treatment; F, unsuccessful.

† Prothrombin times unknown in three.

‡ Prothrombin times unknown in one.

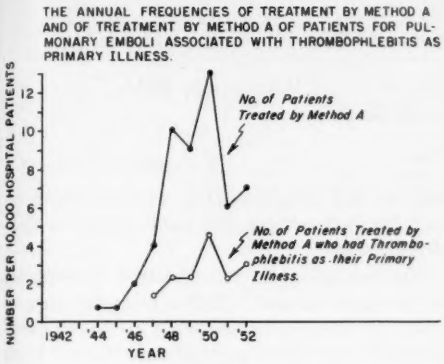

FIG. 3

SUMMARY

1. This study failed to show a beneficial effect of anticoagulant drugs in the treatment of 118 patients with pulmonary emboli when the results of their therapy were compared with the results of the treatment of 112 patients similarly ill for whom no anticoagulant drugs were used.

2. The treatment groups, although not randomly selected, apparently differed only in the years treatment was administered and in the incidence of associated thrombophlebitis. The effect of these differences upon the results were examined and shown not to be the cause of failure to demonstrate a beneficial effect of anticoagulation.

3. The success or failure of treatment could not be related to the plasma prothrombin time values of the patients treated with Dicumarol.

4. Fatal pulmonary emboli occurred as often among patients receiving Dicumarol therapy for pulmonary embolus as among patients treated without anticoagulant drugs.

SUBTOTAL GASTRECTOMY FOR BLEEDING PEPTIC ULCER*

R. V. Bradley, M.D., F. B. Hershey, M.D., S. Schneider, M.D.,
K. B. Coldwater, M.D.

St. Louis, Missouri

Bleeding from duodenal or gastric ulcers is a common and challenging problem. We present the results of our experience with subtotal gastrectomy as treatment for this condition covering a 10-year period ending June 30, 1957.

The records of all cases of bleeding peptic ulcer, and all cases operated on for this disease, were reviewed. This report is concerned with 136 cases in which significant proved hemorrhage was the primary indication for operation. In all but 3 of these cases, the ulcer was removed. Duodenal stump leakage occurred in only 1 case. A mortality rate of 8.1 per cent is reported.

During this 10-year period a fairly consistent policy was followed. All cases were admitted to the surgical service, with close medical collaboration. No case was permitted to die of hemorrhage without an operative attempt at control. Subtotal gastrectomy was completed in all but one case who died of hemorrhage and cardiac arrest during the exploration. The deaths and complications are reviewed and reported. The long term results appear similar to the 529 cases operated on for other indications during the same period and are discussed only briefly in this paper. Other causes of upper gastrointestinal bleeding are not included.

INDICATIONS FOR OPERATION

Nonoperative treatment was planned for the younger patients with their first episode of bleeding which was controlled promptly and who had no other complications of their ulcer. Nonoperative treatment in consultation with our medical colleagues was active and thorough. Medical management of the actively bleeding patient is discussed later.

Patients who hemorrhaged from gastric ulcers were treated aggressively. Unless healing was complete within 10 to 14 days by x-ray, subtotal gastrectomy was performed. If bleeding was massive or did not stop, they were operated on promptly according to the same criteria as duodenal ulcers.

Elective operation was preferred. Seventy-six of the cases stopped bleeding promptly and received at least 6 days' medical treatment in preparation for subtotal gastrectomy. Half of these patients had massive bleeding. For the remainder, hemorrhage was a second complication of the ulceration.

Emergency operation was performed on 43 patients with massive bleeding. For purposes of this paper, emergency operation is defined as operation dictated by inability to bring blood loss under control with nonoperative measures. Of these patients, 13 had bled previously or had some other complication of their ulcer.

Urgent operation was performed in 17 cases. Most of these were patients whose bleeding was not so rapid but who had not stabilized or stopped bleeding within 48 hours after having begun.

Elective operation denotes at least 6 days of patient preparation after control of bleeding. These indications for operation are summarized in table 1. Definitions for massive bleeding, urgent bleeding, and so forth, are given later.

DIAGNOSIS AND MANAGEMENT

As soon as possible and simultaneously with the treatment, the severity of the blood loss is estimated, the most likely site or cause of bleeding is determined, and the patient is observed for persistence of bleeding. The history and physical examination usually suffice to make the diagnosis. Some cases, however, have no previous symptoms of peptic ulcer. If the bleeding stops, upper gastrointestinal x-rays are very accurate and helpful. In massive or continued bleeding, however, their main value is to exclude bleeding esophageal varices. Upper gastrointestinal series was performed before operation in 83 per cent of our cases. If esophageal varices are suspected, the Bromsulphalein retention test has proved useful. Blood ammonia is almost always elevated in

* From the Surgical Services of the United States Veterans Administration Hospital and the Washington University School of Medicine, Department of Surgery, St. Louis, Missouri.

TABLE 1

Indications for subtotal gastrectomy—136 cases

Operative Treatment	Massive Bleeding		Less than Massive Bleeding	
	With previous complications*	No previous complications	With previous complications	No previous complications
Emergency	13	30	None	None
Urgent	3	10	2	2
Elective	21	23	20	12
Total	37	63	22	14

* Complications include pyloric obstruction, hemorrhage and perforation. We usually do not treat pain as a complication.

cirrhosis with varices and should be useful diagnostically in the future. If the diagnosis of bleeding esophageal varices can be excluded, more exact diagnosis is unnecessary. Continued or massive bleeding will require operation whatever the cause. Although exact diagnosis was not made preoperatively in all cases, the cause of bleeding was found and treated at operation in all cases. So-called "blind gastrectomy" was not necessary and was not performed during this 10-year period. Occasionally a rare cause of upper gastrointestinal bleeding was found. We had no difficulties arising from coagulation defects.

Immediately after admission the patient is put at bed rest, given mild sedation and antispasmodics. The initial laboratory work is done and the pulse, blood pressure and respiration are charted as frequently as the clinical condition requires.

A nasogastric tube is useful if the patient has been vomiting. It may suggest the possibility of a coincident pyloric obstruction or gastric retention. It has been useful to us as an indicator of recurrent bleeding. If there is no indication for the tube, antacids and frequent feedings of an appropriate diet are prescribed.

Generous blood replacements are necessary. All the patients in this group demonstrated melena. Some patients enter with severe anemia but apparently normal blood volume, presumably the result of hemodilution during slow blood loss over the course of several days. Blood replacement for these is guided by the hematocrit, signs of continued blood loss and clinical estimates of the cardiac function. Digitalis and transfusion with packed red cells may be necessary to combat venous congestion after patients have had massive hematemesis with syncope or shock from decreased blood volume. With rapid bleeding, hemoglobin concentration and hematocrit are normal until dilution occurs. Transfusion of such patients is guided by the response of the pulse and blood pressure, but frequent hematocrit determinations are also necessary.

For the purposes of this report, patients who demonstrated any two of the following findings are classified as having massive hemorrhage: (1) collapse or syncope, (2) systolic blood pressure less than 100 mm. of mercury, (3) hemoglobin concentration less than 10 gm. per 100 ml. and a proportional decrease in hematocrit, (4) requirement of 2000-ml. blood transfusion, or more, during the first 24 hours to maintain a hemoglobin concentration of 10 gm. per 100 ml. or to maintain normal blood pressure. This group includes patients with both slow and rapid rates of blood loss.

Cases classified as "urgent hemorrhage" required more than 3000-ml. blood transfusions during any 48-hour period to reverse signs of circulatory collapse, maintain the blood pressure at safe levels, and the hemoglobin at 10 gm. per 100 ml.

TECHNIQUE OF SUBTOTAL GASTRECTOMY FOR BLEEDING PEPTIC ULCER

The indications for operation have been outlined earlier and shown in table 1.

Many of the emergency cases were bleeding actively at the time of operation and in most instances an upper midline incision was used to open the abdomen rapidly. Frequently, the site of the bleeding could not be ascertained until the stomach and duodenum were opened. Bleeding was arrested by a stitch in the base of the ulcer to ligate the open artery. Sometimes a long gastrotomy or duodenotomy was necessary and this occasionally revealed some rare cause of the bleeding. However, blind gastrectomy or gastrectomy for hypertrophic gastritis was not necessary in any case during this 10-year period.

There were 118 cases of hemorrhage from duodenal ulcer. In active bleeding the duodenum was opened primarily to control bleeding, before continuing the procedure. The ulcer was removed

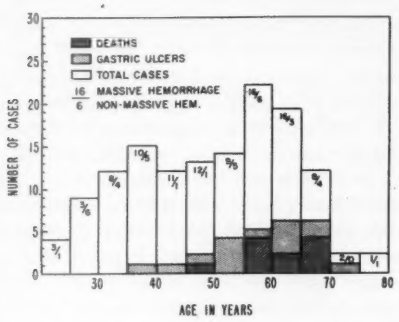

FIG. 1. Age distribution of 136 cases of bleeding peptic ulcer.

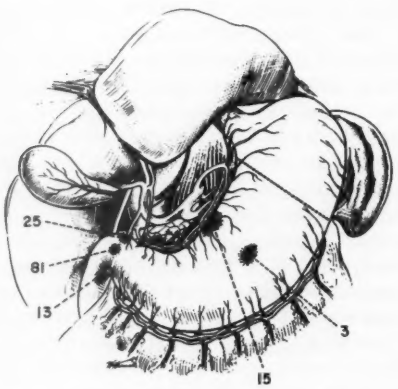

FIG. 2. Distribution of 137 ulcers in 136 patients

in all but 3 cases. Catheter duodenostomy was necessary in 3 cases in which the duodenal closure was insecure. One of these cases (case 1, table 3) was psychotic and on the second hospital day he pulled out the tube and subsequently died of complications. The duodenal stump was not sutured over a clamp, but instead, sutures were placed and tied in the open cuff so that accurate and secure approximation and inversion were achieved without tension. The distribution of the ulcers is shown in figure 2 and it is noted that 81 cases had posterior duodenal ulcers. When duodenostomy was not necessary to stop active bleeding, the anterior wall of the duodenum was preserved and was very helpful in constructing a secure closure.

The resection was the conventional 65 to 75 per cent resection. Distally, the specimen included the pylorus in every case and the ulcer in all but 3 cases. The proximal limit of the resection was the space between the right and left gastroepiploic vessels and the ascending branch of the left gastric artery, as shown by the *dotted line* in figure 2.

Although the resection was standardized in this fashion, other technical features adapted to individual patients were matters of choice among the various surgeons. Some short cuts were used for poor risk patients. Occasionally the omentum was removed. Occasionally the omental vessels were divided outside the arcade. In one case, the infarcted omentum was removed at a secondary operation. Hoffmeister variation of gastrectomy was the usual procedure. Anticolic anastomoses were performed in half the cases. Gastroduodenostomy was performed in 8 cases. Splenectomy was necessary because of capsular tears in 2 cases. In 2 cases, two ulcers were present at operation.

MORBIDITY AND MORTALITY

Of the 136 patients 99 had no postoperative complications; 24 patients, or 11 per cent, had 34 nonfatal complications as listed in table 2. Twelve of these complications required reoperation. One patient was reoperated on for bleeding from an omental arteriole.

Bleeding from the suture line required reoperation on 1 patient and was troublesome enough to require transfusions in 4 other patients. In 1 patient who subsequently died (case 6, table 3), bleeding occurred 24 days postoperatively from a bleeding stomach vessel.

TABLE 2

Nonfatal complications

Reoperation	
Leak duodenal stump	1
Omental infarction	1
Postoperative hemorrhage	2
Wound dehiscence	7
Intestinal obstruction	1
	12
Other	
Thrombophlebitis	3
Pneumonia, pulmonary infarction	4
Postoperative hemorrhage	4
Major wound sepsis	3
Minor wound sepsis	8
	22

TABLE 3

Deaths after subtotal gastrectomy, 8.1%

Case No.	Age	Operation	Site	Comment
			Poor risk patients	
1	46	Emergency	Duodenal	Psychotic; pulled out the duodenostomy tube 2nd postoperative day. Postoperative pancreatitis with abscess and adhesive small bowel obstruction. Died in renal failure after release of bowel obstruction.
2	58	Emergency	Duodenal	Tabetic, bilateral hydronephrosis. Developed cardiac failure, pneumonia, died on 6th postoperative day.
3	60	Emergency	Gastric	Schizophrenia, active pulmonary tuberculosis. Dehiscence 6th postoperative day, major wound sepsis. Convulsion and death on 35th postoperative day.
			Errors in judgment or technique	
4	56	Emergency	Duodenal	G.B*. used to cover stump. Died on 9th postoperative day. Subhepatic abscess-bile-rent in gall bladder.
5	66	Emergency	Duodenal	Large ulcer overlooked at cholecystectomy. Patient dehisced 9th postoperative day, bled massively 14th postoperative day (subtotal gastrectomy) sepsis. Chloromycetin bone marrow depression.
6	66	Emergency	Duodenal	Pulmonary tuberculosis; bled from ulcer of stoma 24 days postoperative; reoperated, rebled, died 12 days later.
			Patients who died of their disease despite treatment	
7	69	Emergency	Duodenal	Refused operation on 3 previous admissions, 4th bleeding episode. Uncontrollable hypotension. Died suddenly 3 hours postoperative.
8	68	Emergency	Duodenal	Patient weighed 300 pounds. Died on table before ulcer could be attacked directly. Cardiac arrest.
9	57	Elective	Duodenal	Massive silent pulmonary embolus. Death 4th postoperative day.
10	64	Emergency	Duodenal	No aortic graft or prosthesis available. Proven duodenal ulcer at 1st operation, aortic aneurysm perforating 3rd duodenal ruptured on 14th postoperative day.
11	66	Emergency	Gastric	Admitted 24 hours after perforation and peritonitis. Perforating and bleeding ulcer. Patient dehisced 8th postoperative day, peritonitis, death.

* The gall bladder serosa was sutured to the closed duodenal stump to form an added layer to closure.

Wound dehiscence was more frequent than we expected. It occurred altogether 10 times including 3 cases who died. This problem deserves more attention.

Eleven deaths occurred with a mortality rate of 8.1 per cent.

Figure 1 shows the age distribution of the 136 cases. It is noteworthy that the deaths occurred

in the older age group except for a poor risk psychotic and the death case 9 who died of pulmonary embolism after an elective gastrectomy. Two deaths occurred in patients with gastric ulcer; the others all had duodenal ulcers. Only 2 deaths can be attributed to technical error at operation.

FOLLOW-UP

Follow-up of these 136 patients varies from 2 to 12 years and resembles the clinical course of ulcer patients treated by subtotal gastrectomy for other indications. Only 2 other patients thus far have developed stomal ulcers. Both were treated successfully by vagectomy. Postgastrectomy symptoms and inability to gain weight are frequent in these veteran patients. Detailed follow-up studies are in progress.

SUMMARY AND CONCLUSIONS

1. During the 10 years ending June 30, 1957, 136 cases of bleeding peptic ulcer were treated by subtotal gastrectomy.

2. Emergency or early operation was performed for 60 cases with massive or persistent bleeding. Elective operation was preferred when time allowed.

3. Hemorrhage was arrested in all but one case by operation.

4. Ten per cent of the patients required reoperation for a surgical complication and 8.1 per cent of the patients died.

5. Only 2 cases of postoperative stomal ulcer have occurred.

6. Review of these cases suggests that less extensive operations might have avoided half of these deaths and complications. Less extensive procedures are reported to be effective and deserve a trial for selected patients.

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A TECHNIQUE FOR INGUINAL AND ILIAC LYMPHADENECTOMY*

KIRKLEY WILLIAMS, M.D., AND HARVEY R. BUTCHER, JR., M.D.

St. Louis, Missouri

Since the description by Stoeckel[30] in 1912 of a combined extra and intraperitoneal operation for the removal of iliac and inguinal lymph nodes, the techniques described for iliac-inguinal nodal dissection have dealt primarily with extraperitoneal dissections,[1-35]. The utilization of both a transperitoneal and an inguinal operation allows the iliac and obturator lymph nodes to be removed more thoroughly. The transperitoneal method also permits the extent of any intra-abdominal metastases to be ascertained and thereby avoids the performance of the operation when metastases are present beyond the limits of the dissection.

THE OPERATION

The peritoneal cavity is examined through a vertical lower abdominal midline incision (fig. 1). If tumor exists beyond the limits of the proposed dissection (proven by frozen section), the procedure is terminated. Large inguinal masses are resected if they are likely to ulcerate before death.

If no intra-abdominal tumor is palpable outside the nodes to be resected, the operation is performed as follows:

1. The dissection is begun at the aortic bifurcation and encompasses a strip of peritoneum, the underlying pelvic soft tissue and the lymph nodes adjacent to the iliac vessels. The peritoneal strip and pelvic areolar tissue is in part disrupted by the removal of the proximal pelvic ureter from it and on the left side by the mobilization of the sigmoid mesentery. Despite the necessity for saving these structures, it usually is possible to maintain the continuity of the fat, areolar tissue and lymph nodes as a single operative specimen extending from the aortic bifurcation to the femoral ring (fig. 2).

All perivascular tissue about the common, external and internal iliac arteries is removed, including the sheaths of the iliac veins. The dorsal extent of the operation along the lateral pelvic wall is defined by the position of the distal pelvic ureter. All soft tissue of the pelvic wall ventral to it is removed. In other words, the hypogastric and obturator nodes are removed completely. The segments of the obturator artery and vein which course through the dorsal portion of the obturator fossa are resected, but the obturator nerve is dissected from the specimen and preserved if the obturator nodes do not contain palpable metastases. The obturator nerve is resected if nodal metastases are attached to it. The intra-abdominal part of the specimen remains attached to the inguinal portion only by the areolar tissue passing beneath the inguinal ligament.

2. The dissection of the inguinal region is begun at the apex of the femoral triangle after an elliptical skin incision is made vertically so that a 4- to 6-cm. width of skin remains attached to the specimen in the area overlying the femoral vessels (fig. 1). The femoral triangle is dissected toward the inguinal ligament in a plane beneath the deep fascia and within the sheaths of the femoral vessels. As the inguinal ligament is approached, the inguinal nodes and fat superficial to it are circumscribed and dissected from the lower border of the inguinal ligament. At this point the planes of dissection are connected with those previously completed within the pelvis and the specimen removed from beneath the inguinal ligament. No difficulty is encountered in passing the pelvic portion of the specimen beneath the inguinal ligament unless it contains a large amount of fat or a lymph node 3 or more cm. in diameter. Should this be the case, the narrow portion of the specimen lying behind the inguinal ligament is divided between clamps and the pelvic nodal mass removed separately. Should this be inadvisable because of metastatic nodes in the femoral canal, the inguinal ligament is severed and then reconstituted after the specimen is removed.

The inguinal skin overlying the inguinal nodes is removed with the specimen (fig. 2) in order to avoid a plane of dissection close to any lymph nodes containing cancer, and to avoid the risk of necrosis associated with thin, wide and poorly vascularized skin flaps. Closure of the skin in

* From the Department of Surgery, Washington University School of Medicine and Barnes Hospital, St. Louis, Missouri.

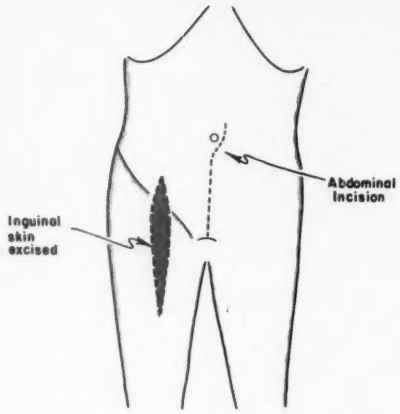

FIG. 1

the area is not a problem unless more than 6 or 7 cm. of skin are excised. These larger defects are closed with the aid of a laterally placed relaxing incision into which a split-thickness cutaneous autograft is placed. Since the institution of the technique of excising the inguinal skin over the region of the vessels, no cutaneous necrosis has been observed.

Before the abdomen is closed, the defect beneath the inguinal ligament is obliterated by suturing the transversalis fascia to Cooper's ligament. The distal end of the transected sartorius muscle may be used to cover the vessels and fill the space behind the inguinal ligament.

A large, firm bulky dressing is applied circumferentially about the thigh and lower abdomen after the cutaneous incisions are closed. Drains are avoided. If suction drainage through a catheter is desired, the catheter should exit through the base of the lateral skin flap rather than through the wound.

For 5 to 7 days postoperatively the patient is kept in bed with the leg and thigh elevated. The leg is wrapped with elastic bandages to the knee; the thigh and inguinal area are encased by a dressing sufficiently bulky and firm to insure immobilization of the wound. If serum or lymph collects in the operative site, it is aspirated, smeared and cultured. Immobilization of the leg by the application of a plaster splint along the entire posterior aspect of the lower extremity is particularly useful in the treatment of groin lymphorrhea. Immobilization reduces any tendency of the wound to fill with lymph unless the fluid is an exudate.

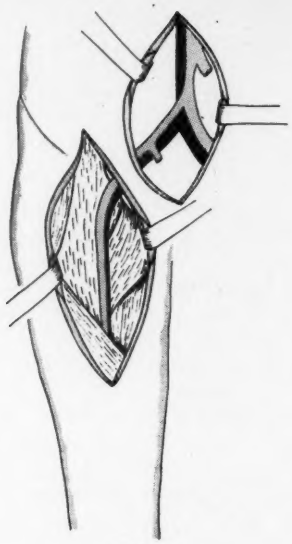

FIG. 2

This technique of radical groin dissection recently has been used successfully in 6 instances. The patients had nodal metastases from melanoma of the pedal skin (2 cases), epidermoid carcinoma of the anal skin (1 case), epidermoid carcinoma of the skin of the leg (2 cases) and adenocarcinoma of the anorectum (1 case).

SUMMARY

A technique for satisfactory *en bloc* resection of the iliac and inguinal lymph nodes is described. The combination of intra-abdominal exploration, transperitoneal iliac nodal dissection and inguinal nodal dissection has two principal advantages:

1. Unnecessary groin dissections can be avoided.

2. The removal of the iliac and obturator lymph nodes is more complete and easier technically.

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PHEOCHROMOCYTOMA IN CHILDREN: A PLAN OF MANAGEMENT AVOIDING HAZARDOUS DIAGNOSTIC TESTS*

JAMES M. STOKES, M.D.

St. Louis, Missouri

The purpose of this paper is to report unusual bilateral pheochromocytomas in a child and to formulate a specific plan of surgical management for children which differs from that commonly used in adults.

CASE REPORT

J. F., (no. 32161), age 9 years, was admitted to St. Louis Children's Hospital on November 8, 1959, because of persistent vomiting.

In September 1959 the child began to vomit several times a week. He was treated for urinary tract infection by antibiotics. He recovered but continued to feel weak and was anorexic. He was hospitalized in his home community for 3 days and received parenteral fluids and antibiotics. The day before his admission to St. Louis Children's Hospital he became lethargic and for intervals of 3 to 5 minutes he did not appear to recognize his parents.

The boy was underweight (24.4 kg., height 53 in.), pale and showed evidence of muscle wasting. A strabismus was apparent and both optic discs were edematous. The pupils were equal and reacted to light normally. The vessels were narrowed but there were no exudates or hemorrhages. He was unable to walk in a straight line and had difficulty walking on the heel and toes. He swayed markedly during the Romberg test but did not fall.

The blood pressure was 170/140 and equal in both upper extremities. The femoral pulses were present and of good volume. The remainder of the physical examination was not abnormal.

Laboratory data. Hemoglobin, 13.8 gm.; hematocrit, 41 per cent; white blood cells, 10,600. Urinalysis: pH 6.5; specific gravity, 1.016; sugar and albumin, negative.

A lumbar puncture was performed; the initial pressure was 170 mm. spinal fluid, the closing pressure was 100 mm., and the spinal fluid was clear. Analysis of the spinal fluid: sugar, 48.8 mg. per 100 ml.; protein, 45.5 mgm. per 100 ml.; chlorides, 120 mEq. per L. Serum electrolyte concentrations were: CO_2, 31 mEq.; chloride, 87; nonprotein nitrogen 23 mg. per 100 ml.; calcium, 11.2 mg. per 100 ml.; phosphorus, 4.0 mg. per 100 ml. Intravenous pyelograms demonstrated prompt excretion of the contrast media without abnormalities in either kidney. The patient excreted 50 per cent of the phenolsulfonphthalein in 15 minutes and 85 per cent in 1 hour.

Intravenous injection of 5 mg. of phentolamine resulted in a precipitous fall of the blood pressure from 170/140 to 120/90. The urinary catechol amine concentration assayed by the rabbit aorta technique[1] was elevated in 2 consecutive tests.

Transabdominal exploration of the adrenal glands was performed after preoperative administration with hydrocortisone and phentolamine infusion during anesthesia. Tumors were found in both adrenal glands (figs. 1 and 2). The left adrenal tumor was about 6 cm. in diameter and could not be separated from the normal gland. Approximately ⅓ of the right adrenal gland remained after removal of the tumor. The blood pressure decreased to 100/60 upon removal of the second pheochromocytoma, and noradrenalin was used intermittently for 24 hours to maintain normotension. After this time the blood pressure stabilized at 130/80 mm. Hg.

Hydrocortisone was administered for 8 days postoperatively in decreasing doses. Twenty-four hour urine output of sodium and potassium was measured until it was evident that no significant adrenal insufficiency existed. The child has not required adrenal supportive therapy since operation. The blood pressure has remained normal since operation and the papilledema has subsided, though there is yet some visual impairment. The patient has gained 30 pounds during the past 11 months, and he is able to participate in school athletic activities for the first time.

The reported incidence of bilateral pheochromocytomas in adults is approximately 10 per cent.[2] Pheochromocytomas are not common in children; the reported cases total about 34.[3] The number of patients with bilateral pheochromocytomas reported in the age group of 0 to 13 years is surprisingly high; 10 of 35 or 28 per cent is the total compared to 10 per cent of those reported in adults. The large number of bilateral

* From the Department of Surgery, Washington University School of Medicine, St. Louis, Missouri.

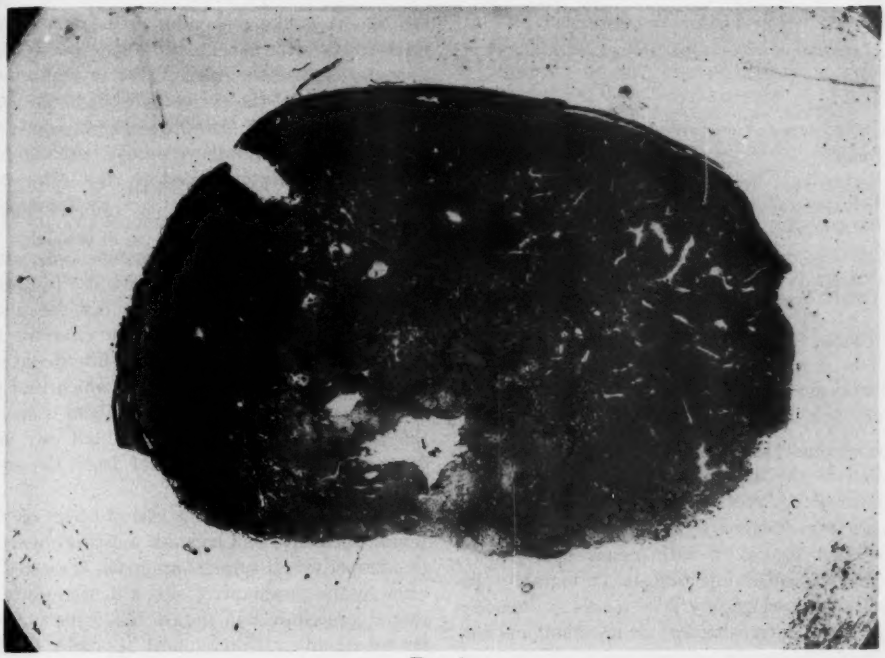

FIG. 1

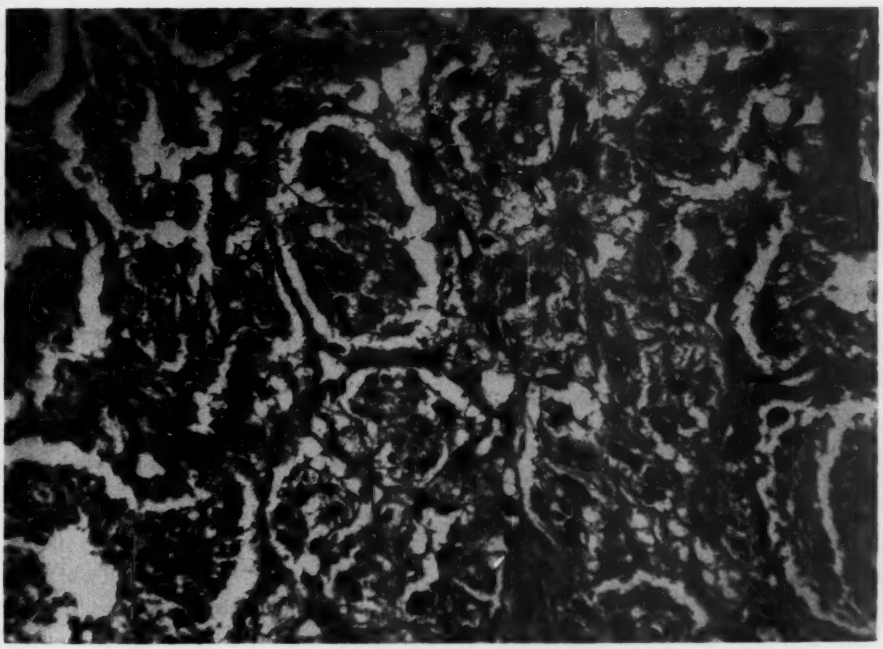

FIG. 2

TABLE 1

*Location of pheochromocytomas in children**

Site	No. of Patients
Adrenal	
Right	12
Left	9
Both	10
Other	5
Total	36*

* From Cone,[3] plus present case report.

† In 2 patients tumors were found in both adrenal glands and in extra-adrenal sites.

pheochromocytomas in children requires modification of the usual diagnostic and therapeutic measures employed to locate the side of origin. These tests designed to localize the tumor before operation consist of intravenous pyelography, retroperitoneal air injection and aortography. Intravenous pyelography is a relatively innocous procedure. Retroperitoneal air injection[4] and aortography,[5] however, are associated with a significant morbidity and mortality for a diagnostic procedure.

Their usefulness must be justified in terms of their accuracy and the possible risk to the patient. The accumulated tabulation of pheochromocytomas occurring simultaneously in both adrenal glands and those arising from chromaffin tissue in extra-adrenal tissue[3] provide data which indicate that retroperitoneal air studies and aortography are not necessary in the preoperative evaluation of children in contrast with adults.

Table 1 summarizes the accumulated pheochromocytomas in children reported by Cone;[3] 10 patients (including this child) had bilateral tumors and in 5 additional patients the tumor arose from sites other than adrenal gland. Thus, the tests designed to identify the side of the tumor would not have resulted in a lateral or posterior surgical approach in these patients. It is questionable whether the tumors arising near the aortic bifurcation and other intraperitoneal sites would have been diagnosed accurately by air studies or aortography. These diagnostic procedures would have added little to the definitive treatment in 14 of the 34 patients (41 per cent), and any test which was false-positive or erroneous with respect to the correct location of the tumors in the remaining 13 patients would further reduce the benefits of these procedures to the surgeon because their value is limited to determination of the correct site (right or left) of the tumor. All the bilateral pheochromocytomas require surgical exposure of both adrenal glands (10 patients); therefore, the retroperitoneal air injection and aortography are superfluous for this group.

The diagnosis of significant numbers of extra-adrenal chromaffin tumors (5 patients) by these tests has yet to be reported. Thus, the use of air injection and aortography is of no value for 15 of the 41 patients. Any errors of interpretation in the remaining 26 examinations which lead to exploration of the wrong adrenal gland utilizing the posterior operative approach and any unsuccessful tests further detract from the usefulness of these procedures.

The determination of the side of origin of the tumor, therefore, is of no value unless a posterior or extraperitoneal surgical approach is used. An error in the presumptive site will necessitate a second procedure and negate the value of this approach; any extraperitoneal approach to the suspected pheochromocytoma prevents the complete exploration necessary to find chromaffin tumors of the paraaortic area and other locations within the abdomen.

The reasons for recommending the abdominal approach in all children with the presumptive diagnosis of pheochromocytoma are: (1) the incidence of bilateral origin of pheochromocytomas in children is high; (2) morbidity and errors are associated with retroperitoneal air studies and aortography in diagnosing this particular tumor in children; (3) transabdominal exploration permits a careful examination of the entire peritoneal cavity for chromaffin tumors arising in extra-adrenal tissue; (4) regional metastases, though infrequent, can be recognized and treated correctly by this method; and (5) the abdominal exposure of the major structures adjacent to the adrenals is preferable to the posterior approach.[6] When this plan of management is used, neither retroperitoneal air studies nor aortography is necessary or desirable.

SUMMARY

The incidence of bilateral occurrence of pheochromocytoma in children appears to differ significantly from that in adults. The transab-

dominal exposure provides access to either adrenal gland or other intraperitoneal sites of chromaffin tumor and it eliminates diagnostic procedures which may be hazardous to the patient. A report of bilateral pheochromocytoma is presented.

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TUMORS OF THE SPINAL CANAL IN CHILDREN*

WILLIAM S. COXE, M.D.

St. Louis, Missouri

The incidence of intraspinal tumors in children is rare when compared to their frequency in adults. Furthermore, under the age of 15 they occur much less frequently than tumors of the brain.[1, 3, 8, 11, 13, 18, 22, 28, 32] Although attention has been drawn to this problem repeatedly in recent years, it is to be hoped that physicians will become increasingly aware of their presence, so that earlier diagnosis and definitive treatment may be accomplished. It is to further this hope that the present study was made.

This report is concerned with 62 intraspinal lesions encountered in children up to 15 years of age, during a 26-year period (1934 to June 1960), on the neurosurgical services of the Barnes and St. Louis Children's Hospitals (table 1). Of these lesions, 27 should be considered as congenital in nature. Several of these cases (congenital dermal sinuses) did not, in fact, have intradural masses in association with the anomaly. They have been included, nevertheless, since they often present with similar findings and symptoms, and in most respects the same surgical considerations obtain. The histologic characteristics of this group will be mentioned below.

The remaining 35 patients included 15 with intramedullary and 20 with extramedullary new growths. Of the former group there were 10 astrocytomas, 3 ependymomas, 1 oligodendroglioma, and 1 intramedullary syrinx, which will be treated in the discussion as a tumor.

A variety of tumors comprise the 20 cases of extramedullary lesions, with a discouraging preponderance of malignancies. Tumors of the brain with seeding into the spinal canal, such as medulloblastomas and ependymomas, have been excluded, as have metastatic tumors not presenting first with symptoms of spinal cord involvement.

Congenital lesions will be considered separately, since the problems encountered in diagnosis and treatment are in many ways different from those with true neoplasia. This category of 27 patients consists of 4 main types of abnormalities: intradural lipomas continuous with a subcutaneous lipomatous mass, teratomatous tumors, congenital dermal sinuses, associated in most instances with intradural dermoid or epidermoid cysts, and one dermoid tumor without a cutaneous defect. Lastly, 2 vascular anomalies of the spinal cord are included, since these lesions are ordinarily considered to be congenital in nature.

CONGENITAL LESIONS

Lipomas

The 9 patients with pure lipomas presented with soft, ill defined lumbar or lumbosacral masses. In addition, several had associated cutaneous abnormalities in the overlying skin, such as small capillary hemangiomas, tufts of hair or small dimples.

Age at the time of admission ranged from 3 months to 11½ years. In 2 cases the masses were reported to have enlarged with age. Only 2 patients presented with significant neurologic impairment, 1 with paresis below the second lumbar area with a comparable sensory level, and the other with motor and sensory deficits below L_5. X-ray examination of the lumbosacral spine revealed either spina bifida, usually of more than one segment, or obvious widening of the spinal canal. In 1 case no x-ray abnormalities were noted.

Total excision was accomplished in 2 cases (table 2). The remainder were partially removed. In the majority of these and similar cases, the lipomatous tissue was intimately entwined with nerve roots or adherent to the surface of a caudally fixed spinal cord, precluding total excision lest grave neurologic injury be done. Of these 9 cases, 6 have remained neurologically unchanged from 1 to 9 years after surgery. One infant suffered damage to several posterior roots on one side at the time of surgery, but to the casual observer, appears completely normal 9 years later. For this reason it has been recommended that a nerve stimulator be used during the dissection of these masses in order to differentiate nerve roots from similarly appearing fibrous

* From the Division of Neurosurgery, Washington University School of Medicine, St. Louis, Missouri.

TABLE 1

Complete list of tumors and other lesions, divided into three categories, arranged according to sex

Type of Lesion	No.	Male	Female
1. Congenital			
Lipomas	9	4	5
Teratoid	7	3	4
Teratomas	2	1	1
Dermal sinus	3	1	2
Dermoid	2	1	1
Epidermoid	2	1	1
Vascular malformation	2	1	1
Total	27	12	15
2. Intramedullary tumors			
Astrocytomas	10	6	4
Ependymomas	3	2	1
Oligodendroglioma	1		1
? Tumor, syrinx	1		1
Total	15	8	7
3. Extramedullary tumors			
Ganglioneuroblastomas	3	2	1
Neuroblastoma	1		1
Ewing's sarcoma	3	2	1
Undifferentiated sarcoma	1	1	
Fibrosarcoma	2	2	
Lymphosarcoma	1	1	
Malignant tumor, unclassified	1	1	
Chloroma	1	1	
Neurofibroma	2	2	
Malignant neurilemmoma	1	1	
Medulloepithelioma	1		1
Metastatic carcinoma	1		1
Reticuloendotheliosis	1		1
Heterotopic glioma (astrocytoma)	1	1	
Total	20	14	6
Total patients	62	34	28

stroma.[17] Two patients were lost to follow-up examination.

Teratomatous Tumors

There is some controversy concerning the proper classification of the abnormalities to be considered here.[4, 14, 16, 20, 24] It is not within the scope of this paper, however, to discuss the problem further. The majority of these 9 lesions, from a gross and microscopic standpoint, might be considered as congenital dysplasias similar to the lipoma and dermoid groups. Perhaps only 2 should be classified as "true teratomas" since they contained tridermic elements in pedunculated masses attached to and involving intradural elements. Of the 7 remaining cases, 6 displayed soft lipomatous masses in the lumbosacral region and for all practical purposes appeared similar to the pure lipomas just mentioned. Two of these contained dermal sinuses, as did the one remaining case without a subcutaneous lipoma; however, upon microscopic examination, all of them contained ectodermal, mesodermal, and other tissue elements less definitely identifiable as endodermal, and thus may be designated as teratoid. The lumbosacral area was the site of all lesions in this series, but teratomas and teratoid tumors may occur in any portion of the spinal canal.[16, 17] Sacrococcygeal teratomas have not been included, since there was no demonstrable involvement of neural structures or their coverings among those seen here.

The age at the time of operation ranged from 1 day to 22 months. As mentioned previously, 2 patients had pedunculated masses attached to the lumbosacral region, being rather large, infected, and associated with a meningomyelocele at its upper pole. Neurologic impairment was present in 3. This was severe in the patient with an associated myelocele, but involved only rectal and bladder sphincters in the other 2.

Six tumors were partially removed and appeared grossly similar to the intradural lipomas previously mentioned (table 2). The 3 totally removed included 2 with dermal sinuses, and 1 pedunculated teratoma attached to the sacral meninges. Four patients were alive without significant neurologic deficit from 1 to 8 years after surgery; 1 died of leukemia, and 1 might be presumed dead because of associated conditions; 3 patients have been lost to follow-up.

Congenital Dermal Sinuses, Dermoids, and Epidermoids

This slightly varied group of 7 patients with congenital lesions included 6 with dermal sinuses with or without dermoid or epidermoid tumors, and 1 with an epidermoid without a cutaneous

TABLE 2

Analysis of congenital lesions

Type	Preoperative Neurologic Deficit		Excision		Postoperative			Follow-up			Duration of Follow-up
	Present	Absent	Total	Partial	Unchanged	Improved	Worse	Alive	Dead	Unknown*	
											yr.
Lipomas	2	7	2	7	8	0	1	7	0	2	
Teratomatous tumors (3 with dermal sinuses)	3	6	3	6	9	0	0	4	1	4	1–8
Dermal sinus without tumor	0	3	3	0	3	0	0	3	0	0	
Dermal sinus with tumor	1	2	2	1	2	1	0	3	0	0	
Epidermoid without sinus	1	0	1	0	0	1	0	1	0	0	
Vascular anomaly	2	0	1	1	0	2	0	2	0	0	2
Total	9	18	12	15	22	4	1	20	1	6	

* Patients never seen again after discharge.

defect. Embryogenetically, these are thought to arise because of improper separation of cutaneous and neuroectoderm cells during early weeks of fetal life.[24, 31] The histopathologic type of lesion seen later may depend upon the time at which the displacement of cutaneous ectodermoidal cells occurred in the embryo. Thus a spectrum of conditions may result from these dysembryonic malformations, varying from a dermal sinus tract only, to tracts that communicate with extradural and subdural dermoids or epidermoids. The latter are more often intradural and may be extra- or intramedullary in location. Dermoids, on the other hand, are rarely intramedullary.[7]

The benign external appearance of dermal sinuses may belie their treachery. Only too often have children suffered repeated episodes of meningitis, back and leg pain, paraparesis or sphincter disturbance before the cause has been discovered. In this series, 6 patients with cutaneous abnormalities ranged in age from 3 months to 2½ years; 4 had had previous bouts of meningitis. One of them developed complete paraplegia several days prior to admission and was found to have two sinus tracts, the lower one ending in a dermoid tumor. This case is described in detail elsewhere.[24] Roentgenograms of the lumbar spine revealed spina bifia and/or widening of the spinal canal in all but 1 case.

When these tracts are discovered early, radical extirpation has been advocated[17, 24, 31] to prevent the obvious dangers of meningitis and/or neurologic damage, should a tumor also be present. In one-half of these patients the sinus tract terminated in an intradural dermoid or epidermoid cyst. In one of these, 2 dermoids were found associated with a single sinus tract. In the majority of our cases complete excision of the intradural tumor was possible; however, tenacious adherence to nerve roots and meninges may prevent total removal. Attempts to do so, under such circumstances, may irreparably damage neighboring nerve structures with unfortunate sequelae.

One patient was seen at the age of 8 years with a 2-year history of irritability, anorexia, back pain and stiffness, lower extremity weakness and atrophy, but no cutaneous abnormality. A very large intradural epidermoid cyst was removed at T_{12}-L_1 and L_2, with dramatic postoperative improvement.

For periods of 1 to 8 years after surgery all have been normal save the 1 admitted paraplegic. This child continues to have lower sacral analgesia and a hypertonic bladder.

Vascular Anomalies

The last 2 cases of vascular anomalies stand apart in sharp contrast to the other congenital lesions. In both cases, one a girl of 15 years, and the other a boy of 10 years, the onset of symptoms was characterized by sudden, sharp back pain,

followed by migratory sensory and motor deficits. One was completely paraplegic at the time of admission and the other severely paraparetic. The girl had numerous nevi over the back, but in the boy, no cutaneous abnormalities were noted. Bloody spinal fluid was found in both, but there was no block to manometric tests. In one the lesion was further localized at the level of D_3 by myelography. This anomaly was removed after electrocoagulation, and the other, arising in the conus, was shriveled by the coagulating current. It was the impression of the operating surgeon that one was an "angioma of the cord" and the other an "angioma, arteriovenous, of the conus."

Postoperatively, the child with the higher lesion was paraplegic for some time, but 2 years later was walking with a cane and had regained bladder control. The boy with the conus anomaly was also last seen 2 years postoperatively, walking without support, but still retaining anesthesia over the entire right leg and the saddle area on the left. Both of these cases have been reported upon in more detail by Trupp and Sachs.[28] They are listed as cases 12 and 23 of that paper.

From the operative descriptions of these 2 lesions, they should probably be classified as vascular malformations, according to the schemes of Turner and Kernohan,[29] Wyburn-Mason,[33] and Rand and Rand.[20]

It has been pointed out by a number of authors that patients with vascular anomalies of the cord may have cutaneous abnormalities in the form of vascular nevi. As was noted in one of our cases, these are often present in the cutaneous dermatome corresponding to the level of the spinal vascular anomaly. The presence of these, in association with findings of spinal cord dysfunction, should certainly heighten one's index of suspicion as to the nature of the cord pathology.

Comments. Our experience with congenital spinal tumors indicates that few present with severe neurologic deficit but, if present, impairment of lower leg and sphincter function is most common. Since, with the exception of the vascular anomalies, we have not encountered patients with lesions above the lumbar region, the reasons for this are obvious. Secondly, all but 2 of the 27 patients had some obvious cutaneous manifestation of the underlying spinal canal involvement. After surgery the neurologic status has usually remained unchanged. In only one instance has it been slightly impaired and in several, improved. In cases with dimples or sinuses, early surgical attack has been emphasized to obviate the complications of infection entering through the tract and/or compression of neural structures by underlying dermoid or epidermoid cysts.

In infants with subcutaneous lipomas noted at birth, further examination should be made after several months. If x-rays reveal spina bifida or widening of the spinal canal, it is quite likely that the lipoma involves intradural structures. It is impossible to state what, if any, neurologic impairment might ensue if these are left untouched. It is presently our feeling that such lesions should be explored and if possible excised. It is assumed that this may prevent either later compression by further growth, or possible damage from caudal fixation of neural tissue by the lipomatous mass. It should again be emphasized that injudicious resection of these tumors is to be condemned.

The symptomatology produced by vascular lesions is, of course, quite variable. Often they may progress over a span of years with periods of remission, or they may become evident within minutes to hours, as in our 2 patients. It would be impossible to discuss surgical treatment in detail, because of the variable pictures which these lesions produce. In those with progressive neurologic deficit, decompression would seem to be indicated. In those of abrupt onset, one is usually forced to do whatever possible to aid restoration of neural function.

NEW GROWTHS OF THE SPINAL CANAL

Thirty-five new growths of the spinal cord or surrounding structures comprise the remainder of the cases in this report. Regardless of their location or histologic type, they share features in common in terms of history, symptomatology, and neurologic dysfunction. However, they have been subdivided into 2 general divisions, intramedullary and extramedullary. The latter are of diverse origin, including intradural and extradural tumors of many types (table 1). Therefore, to designate them as "extramedullary" does not necessarily simplify or elucidate their analysis in a series of this size. It serves primarily to point out features of the intramedullary tumors in sharper relief.

Whatever their neural relationships, many of these tumors offer perplexing diagnostic problems at their inception. The insidious, nonspecific, early symptoms, such as irritability, weight loss, scoliosis, gait disturbance, and back ache, often may lead to erroneous diagnoses. A number of children in this and other series[1, 5, 15, 21, 22, 26] have been treated for months or years as cases of old polio, amyotonia congenita, muscular dystrophy and abdominal tumor. Similarly, the abrupt onset of weakness and sensory loss sometimes lead to other faulty impressions, such as Guillain-Barré syndrome, "transverse myelitis," epidural abscess, hysteria, and the like. It is the rare patient in whom the tumor is discovered before the onset of motor or sensory paresis of some degree. Although diagnostic acumen is always helpful, it may not suffice, for as Ross and Bailey[22] have stated, "the prime requisite for recognition of a spinal cord tumor is suspicion of its existence."

Intramedullary Tumors

As mentioned earlier, this group consists of 10 astrocytomas, 3 ependymomas, 1 oligodendroglioma, and 1 patient with no positive histologic diagnosis, but in whom a syrinx containing brown fluid of high protein content was found in the lower thoracic cord. Other factors in this patient's examination and subsequent course suggested neoplasia rather than just a syrinx formation as the cause of her illness.

There were 8 male patients and 7 female patients. Ages ranged from 6 months to 12 years, with approximately half being over the age of 9 (fig. 1). Half of the tumors involved extensive lengths of the spinal cord; 5 were found from cervical to lumbar segments; 1 cervicothoracic, and 2 thoracolumbar; 4 were confined exclusively to cervical cord, 2 to the thoracic, and 1 to the lumbar region. Thus, 10 of the 15 gliomas involved the cervical cord alone or together with other segments (table 3).

The average duration of symptoms before admission to the hospital was 24 months. Initial symptoms were often nonspecific. Practically all, at one time or another, were described as "irritable." This description may stem, in large part, from the high incidence of pain, rigidity and stiffness of neck or back muscles. The significance of these complaints has recently been emphasized by Richardson.[21] In 10 patients these were the earliest and most persistent findings, but eventually all but 1 developed these complaints. Two patients were noted to have mild scoliosis 1 to 3 years before the onset of more alarming symptoms; 2 others experienced difficulty walking from 5 to 7 years before admission, one being regarded as "retarded," and another as suffering from muscular dystrophy. One most interesting patient, with a high cervical cord astrocytoma, had been treated for unilateral bronchiectasis for 3 years. It had been noted elsewhere that the

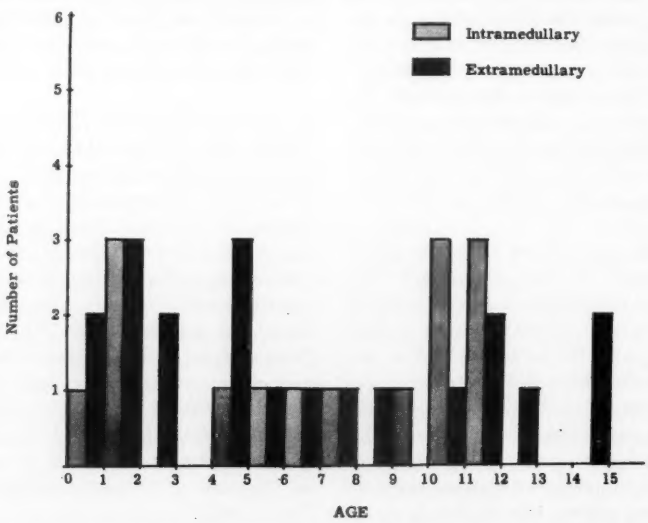

FIG. 1. Age at time of admission with intramedullary and extramedullary tumors

TABLE 3

*Frequency at various sites of 35 intra- and extramedullary new growths**

Location of Tumors	Intramedullary			Extramedullary		
	No.	%	Total	No.	%	Total
Cervical	4	27	47	3	15	70
Thoracic	2	13		8	40	
Lumbar	1	7		3	15	
Cervicothoracic	1	7	53			30
Thoracolumbar	2	13		4	20	
Cervico-thoraco-lumbar	5	33		2	10	
Total	15			20		

* Note extensive length of intramedullary tumors in contrast to more limited distribution of extramedullary tumors.

left diaphragm moved poorly. Only much later, when pain, paresis and muscular atrophy developed, was the etiology determined.

At the time of admission here, 14 of the 15 patients with gliomas had obvious paresis of 1 or more extremities, depending, of course, upon the location of the tumor. Motor loss varied from mild weakness of 1 extremity to virtual quadriplegia with respiratory embarrassment. Sensory deficits were difficult to establish with certainty in some children, because of their age and irritability. In general, sensory loss was more apparent in patients with cervical cord involvement than in those with tumors at lower levels.

Pain of a radicular character was definitely described by 4 patients. Hyperhidrosis of the head and neck was noted in 3 with cervical or high thoracic tumors. Bladder and anal sphincter paresis was present in only 3 cases. Reflex activity was variable. Pathologic tendon jerks of either low or increased activity were found in all. Both were frequently found in patients with tumors of extensive length.

Of great interest were 2 patients presenting with signs of marked increased intracranial pressure. Both had sprung cranial sutures, vomiting, optic atrophy and/or papilledema. Each was thought to have a cerebellar tumor until ventriculography and exploration revealed extensive arachnoiditis of the posterior fossa. Mention will be made of this finding later.

Diagnostic studies. Further study of the spinal canal by x-ray, lumbar puncture and myelography was indispensable in arriving at the correct diagnosis (table 4). Plain spine films revealed pedicle erosion or widening of one or more segments of the canal in 10 patients. In 2 of these patients, subluxation of the second cervical vertebra on the third was noted, both harboring extensive cervico-thoraco-lumbar tumors. At the time of lumbar puncture, 9 showed complete block and 3, partial block to cuff manometrics. Xanthochromia of the spinal fluid was noted in 8, but the protein content was elevated in all 15, ranging from a borderline 45.3 mg. per 100 ml. to 1000 mg. per 100 ml. Out of 15 patients, 14 were over 100 mg. per 100 ml.

Lumbar myelography was performed in 12 patients, and cisternal in 2. In all cases satisfactory tumor localization was obtained, although in instances of complete block of the subarachnoid space, the rostrocaudal extent of the tumor could be learned only by further neurologic, x-ray, and surgical evidence. Ventriculography was the only contrast study utilized in 1 patient with neurologic and x-ray evidence of an upper cervical cord medulla tumor.

Surgical treatment. Laminectomy was performed upon all patients, visualizing the lesion in every instance. A small biopsy was taken in 3, partial excision of the tumor mass was carried out 8 times, and in 3, near total excision was accomplished. Our usual practice has been to leave the dura open over the area of swollen cord for further decompressive effect, particularly if very little tumor was removed; however, in 4 patients it was closed tightly.

TABLE 4

Value of diagnostic studies in 35 patients with new growths of spinal canal

Examination	No. Patients Undergoing Examination	Abnormal Findings	
		No.	%*
Spine films	35	24	66.6
Lumbar puncture	30		
Manometric block		26	86.6
Abnormal color or protein content		24	80.0†
Myelography	26		
Positive		26	100

* Percentages based on number subjected to study and not on total number of patients.

† Insufficient fluid obtained for analysis in 20 per cent of the cases studied.

Associated pathologic findings were frequently encountered. In 8 patients, all with histologically verified tumors, a syrinx was found in or adjacent to the tumor. One patient included in this group did not have a positive tissue diagnosis. At laminectomy thick yellow fluid was aspirated from a swollen thoracic cord. It is possible that this cavity lay distal to an intramedullary tumor mass, as her subsequent course indicated progressive cervical cord involvement, leading to death 6 months later. The frequent association of syringomyelia and tumors of the spinal cord has been the subject of a recent review by Poser.[19]

As alluded to earlier, extensive posterior fossa arachnoiditis was found in 2 patients presenting with symptoms and findings of increased intracranial pressure. These 2 boys, both of whom had extensive astrocytomas, and 1 girl with an oligodendroglioma of the cervico-thoracic cord, were found to have amazingly dense arachnoidal thickening overlying large portions of the cord or cauda equina. In the child with the oligodendroglioma, the arachnoiditis was found at thoracic laminectomy elsewhere, 3 years before a cervical laminectomy performed here. Sharp dissection was required to remove the tissue which was several millimeters thick. In the cervical cord, the only abnormality was the tumor itself. In one of the boys, following posterior fossa exploration, this change was found in the thoracolumbar theca, overlying an astrocytoma of the thoracic cord and cauda equina. In the remaining case of astrocytoma, the degree of thickening can best be appreciated by the illustration (fig. 2). These pieces of tissue were shaved, using sharp dissection, from the dorsal surface of the spinal cord exposed from C_4 through L_1. Unfortunately, this process extended completely around the cord, embedded all the roots, and precluded extensive resection. Histologically this appeared to be dense, fibrous, collagenous tissue, containing inflammatory cells within its stroma. The cause of this reaction remains obscure, but such findings have not been described in the many reported series similar to this one.

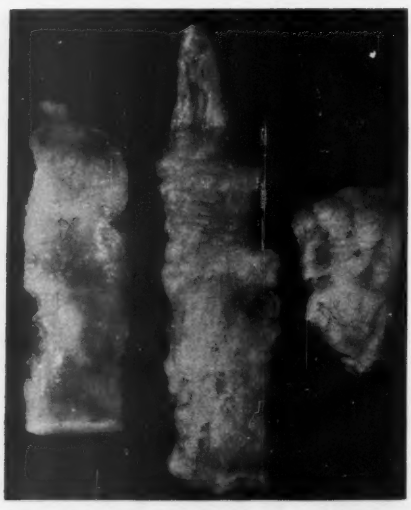

FIG. 2. Pieces of thickened arachnoid removed from dorsal surface of spinal cord, exposed from C_4 to L_1, in a 2-year-old boy. Width of portions shown is approximate width of underlying cord containing extensive astrocytoma.

During the early postoperative period 8 patients improved, 6 remained essentially unchanged, and 1 became worse, dying within 2 weeks. This patient's tumor was the most rostrally situated, extending from the upper cervical cord into the medulla. The period of follow-up examination is variable; 6 patients were alive, without significant neurologic deficit from 1 to 8 years after discharge; however, 2 of these, though well 5 and 8 years after surgery, have not been seen for 6 years. Their fate is therefore unknown. One is alive with slight deficit 1 year after surgery, but 8 are known dead; 1 death occurred 2 weeks postoperatively, 4 within 1 year, 1 in under 3 years, but 1 lived for 5 and another for 6 years (table 5).

Postoperative x-ray therapy was administered to 7 patients. It is noteworthy that of the 6 patients living and well at the time of last examination, 5 received this treatment. At autopsy, of the remaining 2, 1 had extensive ependymoma implants throughout the entire ventricular system, as well as the spinal canal. Only the spinal cord was irradiated in this patient, since initial symptoms were referable to this area alone. The other patient receiving radiation therapy survived the longest of those known dead. This would seem to support the belief of Wood *et al.*,[32] that regardless of the low grade histologic appearance of these tumors, x-ray therapy is of considerable benefit.

Comment: Patients with gliomas of the spinal cord comprise the largest single group in this and other series.[13, 19] Often they creep upon the scene in odd disguise and with characteristic in-

TABLE 5

Present known status of all patients in series

Category	No.	Alive without Symptoms	Alive with Symptoms	Dead	Probably Dead	Unknown
Congenital	27	12	5	1	1	8
Intramedullary	15	4	1	8		2
Extramedullary	20	2	2	14		2
Total	62	18	8	23	1	12*

* Of these 12, many might be presumed alive and well.

sidiousness, before a combination of complaints and findings rings the bell. Many years ago, Gowers and Horsley[11] stressed the importance of the sequence of symptoms seen in spinal neoplasms. They pointed out with emphasis that in both extradural and intradural tumors, the sequence is "pain, motor paralysis, sensory paralysis." It is worthwhile to emphasize once again the unfailing significance of epaxial muscle rigidity, spasm and pain, with or without motor weakness, as frequent early concomitants of spinal tumors.

A word might be said also about the presence of papilledema with spinal cord tumors. Their association has been known for some time,[10, 18] although in some patients, this is readily explained by the high cervical location of the tumor. It has also been proposed that the high protein content of the spinal fluid delays absorption by the clogging of blood-brain barrier pores with protein molecules, resulting in a larger spinal fluid volume within the subarachnoid space. This, in turn, would cause increased pressure, hydrocephalus and papilledema. In our 2 patients the cause was readily seen at the time of surgery. In each the entire ventricular system, including the fourth ventricle, was dilated. It was felt that the arachnoiditis or thickening was so pronounced that normal fluid flow was impossible. In neither was there any evidence of tumor involving the cerebellum, medulla or upper cervical cord at the time of posterior fossa exploration. The diagnosis in one was atresia, or postinflammatory obstruction, of the foramina of Magendie and Luschka. The cerebrospinal fluid was later diverted to the cardiac atrium, using a Holter valve mechanism. In addition to these findings, both patients had sufficient evidence of spinal tumors to warrant independent investigation of the spinal canal.

Once suspicion is aroused, more definitive diagnostic aids must be used in the hope that earlier, definitive treatment be instituted, thus preventing needless years of suffering and the ravages of progressive neural damage.

Surgical treatment should be aimed at adequate decompression of functioning or potentially functioning spinal cord. It should again be noted that half of these tumors extended through more than one anatomical area of the cord, thus requiring extensive laminal removal to effect adequate exposure. In a few instances of well delimited ependymomas of the cervical cord, complete gross removal will be possible. The same is true of similar lesions of the cauda equina, though none were seen in this series that did not also invade the intramedullary region. Most of the astrocytomas were adherent to surrounding cord tissue, preventing more than partial removal or biopsy. The dura should be left open over swollen areas if myelotomy has not been productive of internal decompression. No "two stage"[9] procedures in the usual sense have been carried out in this series.

Although patients with gliomas may have characteristically indolent courses, there is some evidence that x-ray therapy may increase longevity and, in some cases, may prove curative.[22] The trend, in our experience, supports this impression, but it is not of sufficient size to be more definitive.

Extramedullary Tumors

This group of 20 patients, though constituting the larger portion of noncongenital lesions, includes 14 types of tumors (table 1). The high incidence of malignancy lends cohesion to their analysis, but the limited value of this method is fully appreciated when considering such a mélange of tumors. Since space will not permit extensive discussion of each type, the interested reader is referred to the recent comprehensive review of the entire subject by Rand and Rand.[20]

The ratio of male to female patients was found to be slightly over 2:1. Age at the time of admission ranged from 5 months, in a child with an undifferentiated extradural sarcoma, to 15 years, in a boy with a malignant neurilemmoma (fig. 1). In general, these tumors tended to be rather localized along the spinal axis (table 3); 8 were exclusively thoracic, 3 cervical, 3 lumbar, and 4

thoraco-lumbar. One child with Von Recklinghausen's disease had multiple intradural neurilemmomas throughout the spinal axis. The only extramedullary astrocytoma occurring in the series was found to occupy virtually all of the subarachnoid space over the brain and spinal cord at postmortem.

Symptoms. Again, the most prominent initial symptoms in this group were pain or discomfort in the back or neck. In infants, marked irritability and crying, particularly when handled or examined, was apparent to both parents and physicians. Even so, in both younger and older children weakness of 1 or more extremities was an early concomitant of painful spinal rigidity or occurred without any discomfort whatsoever. Considerably less frequent, as initial complaints, were radicular pain, incontinence of urine, constipation and rectal prolapse, the latter 2 noted in several infants. Ultimately, at the time of admission, ¾ of the patients were found to have definite epaxial muscle rigidity, spasm or pain on movement. It is of interest to note that 3 of the 5 exceptions to this had tumors of the neuroblastoma type, a finding recently commented upon by Rand and Rand.[20] Of the 20, 17 complained of or were noted to have paresis or paralysis of one or more extremities. In fact, ½ of the entire group were paraplegic when first seen here. A history of trauma immediately preceding the onset of other symptoms was obtained in 3, whereas fever, malaise and fatigue preceded further symptoms in several patients with sarcomas and leukemia.

As might be predicted, in a large segment of this group the time lapse between the first symptoms and grave neurologic impairment was brief. In 80 per cent the duration was less than 4 months. In approximately 25 per cent signs of paralysis were obvious for less than 5 days before admission. When the characteristically benign tumors, *i.e.*, 3 nerve sheath tumors and reticuloendotheliosis of the cervical spine, are excluded, the abruptness of onset becomes even more dramatic.

In addition to the motor loss noted upon admission, sensory deficits were more easily detected in these patients than in the glioma group. Approximately half of 15 with sensory loss showed definite dermatome levels or deficits of great localizing value. Again, the great majority of these patients proved to have malignant tumors.

Reflex patterns were to some extent related to the nature of the lesion, its location and duration of symptoms; 10 patients showed absent or very hypoactive tendon jerks in both legs. All of these patients harbored malignant tumors, producing relatively rapid compression of the cord or cauda equina. Nine patients with brisk lower extremity reflexes included 3 with nerve sheath tumors, 1 heterotopic glioma, and sarcomas occurring at high cord levels.

Diagnostic aids. Roentgenographic changes were of invaluable aid in arriving at the proper diagnosis. Taken as a group, a multiplicity of pathologic changes were found in 14 of the 20 patients. These findings were as follows: widening of the spinal canal in 2, pedicle erosion in 7, and changes in vertebral body density or height in 5. Mediastinal masses were useful clues in 3 cases of ganglioneuroblastoma, as well as 1 case of neurofibromatosis; 6 patients had no abnormal x-ray findings (table 4).

Invaluable data were obtained by analysis of spinal fluid dynamics, content and myelography. Lumbar puncture was performed upon all but 5 patients. Complete block to jugular compression was discovered in 11 and partial blocks in 3. Xanthochromia, or elevation of the protein content, was described in 9. In the remaining 6, either no fluid could be obtained or the amount was insufficient for analysis. Protein values ranged from 78 mg. per 100 ml. to 3600 mg. per 100 ml. Myelography was considered indicated in 12 patients, positively localizing the lesion in all cases. The cisternal route was used 4 times and the lumbar 8 times.

Fifteen patients underwent laminectomy, with removal of as much tumor tissue as possible. In 2 patients with nerve sheath tumors total excision was accomplished, although one of these had numerous, similar intraspinal lesions. Biopsy through a thoracotomy was performed upon 2 of the ganglioneuroblastomas. In 3 patients with lymphosarcoma, chloromatous leukemia and Ewing's sarcoma, no surgery upon the cord was performed. No tissue diagnosis was made in the case of Ewing's sarcoma, x-ray changes alone being relied upon.

During the immediate postoperative period, 10 of these patients experienced gratifying improvement, 4 remained unchanged, and 1 became worse. Of the 2 subjected to thoracotomy, 1 died of cardiac arrest at the conclusion of the

operation and the other became progressively worse until death 8 months later.

Radiation therapy was utilized in 13 patients. Neurofibromas were obviously not irradiated, even though 1 proved later to be malignant. Neither case of lymphosarcoma or chloromatous leukemia was treated because of rapid, widespread progression.

The ultimate, dismal survival rate in this group is not unexpected; 2 are alive and without neurologic deficit 18 months and 1 year after treatment, respectively. The respective diagnoses are neuroblastoma and undifferentiated sarcoma. Alive with slight neurologic deficit, but severe scoliosis, is 1 boy with a ganglioneuroblastoma of the thoracic spine, 7 years after surgery and radiation therapy. One 3-year-old girl with reticuloendotheliosis of the cervical spine and left acetabulum is alive but continues to have neck pain 1 year after partial excision of the spine lesion and one course of x-ray therapy to both sites. She has recently received another period of radiation treatment to the cervical spine. One child with a large cervical neurofibroma was a victim of neglect, both before and for 7 years after surgery. He was severely incapacitated when last seen 15 years ago. One child with an extradural fibrosarcoma has been lost to follow-up, though he was without any neurologic symptoms, both before and after excision. The 1 patient with an excellent postoperative prognosis was killed in a tractor accident 4 years after excision of a solitary neurilemmoma at T_2.

The 12 remaining patients were all dead within 1 month to 1 year. It will be recalled that 1 patient died at surgery. Thus, only 20 per cent of this group are known to survive, 70 per cent are known to be dead as a result of their disease, and for 10 per cent, the outcome is either unknown or death was not related to the tumor (table 5).

Comments. Unfortunately, we have not been privileged to treat a large number of children with benign tumors, though this has been the occasional experience of others.[26] Among the extramedullary group only 5 were intradural and 3 of these were nerve sheath tumors, 1 of which was malignant. Ordinarily, the prognosis of patients with neurofibromas or neurilemmomas is excellent. Therefore, every attempt should be made to effect prompt diagnosis and complete extirpation whenever possible. Of the remaining 2 intradural tumors, 1 proved to be a highly malignant medulloepithelioma and the other, chloromatous leukemia with extensive intra- and extradural masses of tumor.

Although tumors of the neuroblastoma group are usually considered highly malignant, the prognosis may be quite good, especially when seen at a very early age; 2 of the 4 patients in this series have survived 7 and 1½ years, respectively. Both were initially seen at approximately 1 year of age. Vigorous therapy should be directed first at relieving nerve or cord compression by surgery and second, by the use of x-ray therapy. These methods of treatment will often result in long periods of survival and possible cure.[20, 23, 30] The majority of the remaining cases were malignant extradural sarcomas. Here, the best one can hope to achieve is palliation with surgery and radiation therapy. The same may be said for metastatic carcinoma of the spine.

Reticuloendotheliosis (eosinophilic granuloma) of the spine is exceedingly rare. These are not true neoplasms, but by virtue of their location may produce signs of cord compression, which might occur after collapse of vertebral bodies. Although spontaneous resolution may sometimes occur, it is usually recommended that they be curetted or irradiated. The outcome in our 1 case is uncertain at the moment.

Finally, there was 1 case of primary extramedullary astrocytoma. At postmortem examination the entire spinal and intracranial subarachnoid space was filled with tumor tissue. Cooper and Kernohan[6] have recently reviewed the subject of the origin of these tumors. It is their belief, as well as that of others,[2] that these tumors arise from heterotopic glial cells within the subarachnoid space that have undergone neoplastic changes. There would seem little to offer a patient such as ours in the way of definitive therapy unless it would be x-ray therapy to the entire nervous system. Those in whom the tumor occurs in more limited sites have fared better with local surgery and postoperative radiation treatment.[20]

CONCLUSION

As was stated at the beginning of this paper, it is our hope that the presentation of our experience with spinal tumors in children might in some way hasten the diagnosis and treatment of these patients. In each category discussed, an

attempt has been made to focus attention upon certain salient features of their histories, symptomatology, physical findings and therapy. In certain of the congenital lesions the diagnosis may be immediately apparent at birth from the presence of obvious masses, either pedunculated or subcutaneous. Neurologic findings are usually absent or slight and therapy may be considered with leisure. On the other hand, subtle, easily overlooked cutaneous defects should be searched for with diligence. As witness to this effort, it should be mentioned that only in the last 2 congenital dermal sinus excisions in this hospital, was there no history of previous meningitis.

With regard to patients suffering from intramedullary gliomas, awareness and suspicion of tumors may be the prime requisites in arriving at the correct diagnosis. The duration of vague but significant symptoms may be extraordinary. All too often the irritability, muscle spasm and rigidity, scoliosis, pain, and even weakness, are ascribed to other causes. Other more bizarre symptom complexes, such as hemidiaphragm paresis with long standing bronchiectasis, pneumonia, and increased intracranial pressure, have puzzled the physician for months or years before the true cause was determined.

In the nongliomatous tumors of extramedullary origin, the majority in our experience was with extradural malignancies of one type or another. Their presence is heralded by the same, but relatively abrupt, onset of symptoms and signs. Although this may suggest a poor prognosis, it should in no way slow the search for the cause. Once these tumors are suspected, every aid should be utilized to establish the diagnosis. Careful examination of spine films will often reveal slight but definite abnormalities. If obvious erosion of bony structures or widening of the spinal canal is not apparent, the interpediculate distances should be carefully measured and plotted against normal values.[31] Retrospective analysis has often revealed changes missed at first glance. Spinal fluid examination has almost invariably produced evidence of the tumor within, either from manometric block or abnormal protein values. Myelography should be done in practically every case to confirm and localize absolutely the limits of the tumor.

After myelography, surgical decompression of the cord should be carried out as soon as possible. Although total removal of tumors is desirable and sometimes possible, respect for surrounding neural tissue must be the prime consideration if the tissue is not easily dissected. Adequate bony and/or dural decompression may then be followed by roentgenotherapy to the involved cord, with good hope of improvement. In a number of cases, depending of course upon the histologic nature of the tumor, patients may be cured or relieved of symptoms for many years (table 5).

SUMMARY

1. Sixty-two patients under the age of 15, with lesions of the spinal canal, have been treated on the neurosurgical service of this hospital during the past 26 years (1934 to 1960).

2. Only patients with neurologic or anatomical evidence of spinal cord and/or cauda equina involvement have been included in this report.

3. Three broad categories of cases have been derived from this material. These include 27 cases of congenital lesions of various types, 15 intramedullary tumors, 14 of which were proved gliomas, and 20 extramedullary tumors.

4. Attention has been drawn to certain significant features in each group pertaining to history, physical examination, therapy and survival.

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MORTALITY AND MORBIDITY ASSOCIATED WITH RESECTION OF PANCREATICODUODENAL CANCERS

WILLIAM T. NEWTON, M.D.*

St. Louis, Missouri

Mortality reported for pancreaticoduodenectomy in the United States has ranged as high as 47 per cent.[6, 8, 10, 11] Recently, however, a few individual surgeons[3, 12, 15] have reported mortality rates below 20 per cent. These reports have encouraged critical review of the results at other institutions.

At Barnes Hospital, resection of the head of the pancreas and duodenum for malignant neoplasms has been performed by a number of surgeons of both the attending and resident staffs. Mortality and morbidity have been high. This report is a critical attempt to determine the factors responsible for the morbidity and mortality of pancreaticoduodenectomy. The records of all resections of the pancreas and duodenum for malignant neoplasms at Barnes Hospital from January 1, 1950, to January 1, 1960, were studied.

The features of the 18 survivors are summarized in table 1; those of the 16 who died after resection are summarized in table 2. A standard form of pancreaticoduodenectomy for cancer of the head of the pancreas or periampullary area was performed in 28 patients with 11 operative deaths (39 per cent). Six operations representing extension of the standard pancreaticoduodenectomy with resection of the entire pancreas or contiguous organs were performed with five deaths. The ages of the patients varied from 17 to 79 years with a mean age of 58 years. There were 20 men and 14 women in the total series.

A review of the operative deaths (table 2) shows that sepsis was the cause of death in 8 of 16. Two patients (cases 8 and 24) had gangrene of the intestine as the cause of sepsis, and in 3, disruption of an anastomosis was the cause. The origin of the sepsis in the remaining 3 is unknown. Uncontrollable hemorrhage from small vessels within the area of the resection was responsible for 6 deaths. In case 32 a blood coagulation defect was the evident cause of uncontrolled hemorrhage. In the other 5 cases the bleeding was related to faults in operative technique. Among miscellaneous causes of death were heart failure and pulmonary edema (case 18), and sudden, massive, immediately fatal hematemesis on the 23rd postoperative day (case 27).

Among the survivors (table 1) sepsis was the major cause of morbidity. Only 8 of the 18 survivors recovered without being troubled by an infection. Disruption of an anastomosis was the apparent cause of ½ of the infections. Only 2 of the 18 had completely uncomplicated postoperative courses.

OPERATIVE MANAGEMENT

Determination of operability. The records indicated that the criteria of operability were superseded in 14 operations. This led to such maneuvers to get out of trouble as venous autograft bridging of a defect of the portal vein, the occlusion of the portal vein for a considerable length of time while the tumor was being dissected from the vein, and leaving visible cancer in the body because it was found impossible to remove it after taking irrevocable operative steps. Of the 14 patients in whom criteria of operability were extended, 10 died. In this group the operations were especially long, hemorrhage was profuse and much blood was transfused. Hemorrhage of dark blood from raw surfaces and profound hypotension in spite of what appeared to be adequate blood replacement especially characterized those cases in which the portal vein had to be temporarily occluded. The pooling of blood in the splanchnic veins evidently was the cause of this hemorrhage and sudden profound hypotension. The validity of this explanation is supported by the following observations. In a case not reported in this series it was necessary to occlude the portal vein in order to control bleeding from it. Dark venous bleeding almost immediately appeared from many small vessels in the operative field, and the blood pressure quickly fell. An examination of the small

* John Cochran Veterans Hospital, 915 North Grand Avenue, St. Louis 6, Missouri.

From the Department of Surgery, Washington University School of Medicine, St. Louis, 10, Missouri.

TABLE 1

Clinical features of survivors after pancreaticoduodenal resections

Case No.	Age, Sex	Primary Site of Tumor*	Operative Management				Postoperative Complication	Postoperative Hospital Stay	Survival
			Pancreatic remnant	Operating time	Blood given	Indications for resection extended?			
				hr	*units*			*days*	*mo.*
1	69, M	Panc.	End-to-side	6¼	5	No	Prolonged ileus	22	3
2	51, M	Panc.	Duct-to-side	7¼	6	Tumor at line of resection	Subhepatic abscess	20	37
4	52, F	Amp.	Closed	5	3	No	Pancreatic fistula	22	23
6	57, M	Amp.	End-to-side	5	3	No	Disruption pancreaticojejunal anastomosis, hematemesis	38	46
9	44, F	Panc.	End-to-side	5½	6	Portal vein torn, tumor at line of resection	Prolonged ileus	14	6
13	36, F	Amp.	End-to-side	6¼	6	No	Fever, slow lysis	39	12
14	79, F	Amp.	End-to-side	4½	6	No	Biliary fistula	52	50
15	49, M	Amp.	End-to-side	6	4	No	None	16	51
17	64, F	Panc.	End-to-side	7½	4	No	None	16	8
19	67, M	Panc.	Resected	6½	4	Peripancreatic extension	Biliary fistula	15	15
20	64, M	Panc.	Duct-to-side	3½	4	No	Subhepatic abscess	14	8
21	70, M	Panc.	End-to-side	?	4	Tumor adherent to portal vein	Hemorrhage, obstruction, gastrojejunostomy	48	19
23	42, F	Duod.	End-to-end	5	4	No	Fever, slow lysis	38	48†
26	63, M	Amp.	Duct-to-side	6	4	No	Liver failure, subphrenic abscess	51	3
29	17, M	Amp.	Duct-to-side	6½	5	No	Intestinal obstruction	30	27†
31	70, F	Panc.	Duct-to-side	7	4	No	Subhepatic abscess	28	6
33	49, F	Panc.	End-to-end	4¾	4	No	Pancreatic fistula	21	7
34	74, M	Panc.	Duct-to-side	4	3	No	Obstruction at gastrojejunostomy	38	9

* Abbreviations: Panc., head of pancreas; Amp., ampulla of Vater; Duod., duodenum.
† Alive and well.

intestine showed dark congested venules over the surface of the entire small bowel and in the adjacent mesentery. The superior mesenteric artery was then occluded near its origin in order to stop the flow of blood into the overly distended splanchnic system. After this occlusion, venous bleeding slowed perceptibly and the blood pressure rose slowly from 70 to 90 mm. Hg. After flow was restored through the mesenteric artery and the portal vein, the blood pressure quickly rose to 130 mm. Hg without further blood transfusion. The congested veins in the bowel emptied very rapidly.

Obviously one of the most important causes of morbidity and mortality of pancreaticoduodenectomy is attempting the procedure when clear indications of inoperability exist. This may be prevented by an orderly, stepwise determination of operability. After a general abdominal exploration has shown a mass in the periampullary area but has failed to demonstrate distant metastases, the biliary tract is first examined. The surgeon should be wary of making a diagnosis of cancer in the absence of distention of the biliary tract. All of the cases in this series showed distention of the biliary system. This was true even

in case 29 in which jaundice was not present, and cancer of the ampulla of Vater was an unexpected finding at operation for another unrelated disease. As the next step, the surgeon should make a careful examination of the regional lymph nodes. Biopsy should be done on the slightest suspicion of metastatic cancer.[11] Next, a Kocher maneuver is performed to demonstrate freedom from pos-

TABLE 2

Clinical features of operative deaths after pancreaticoduodenal resections

Case No.	Age, Sex	Primary Site of Tumor*	Operative Management				Survival	Postoperative Complications
			Pancreatic remnant	Operating time	Blood given	Indications for resection extended?		
				hr.	*units*		*days*	
3	69, M	C.B.D.	Closed	5½	6	No	21	Pancreatic fistula, disruption choledochojejunal anastomosis
5	71, M	C.B.D.	Closed	5	3	No	10	Fever, azotemia, no autopsy
7	60, M	Amp.	End-to-side	4¼	3	No	6	Disruption pancreaticojejunal anastomosis, peritonitis
8	72, F	Panc.	End-to-side	6½	4	Tumor at line of resection	16	Superior mesenteric artery occlusion, gangrene of small intestine
10	38, F	Panc.	End-to-end	9½	20	Portal vein torn, tumor in wall of vein	6	Sustained high fever, no autopsy
11	70, M	Panc.	End-to-side	7	12	Portal vein torn, tumor at line of resection	2	Hemorrhage
12	67, M	Panc.	End-to-side	10½	9	Portion of portal vein resected, extension to colon	6	Persistent hemorrhage from drain sites, oliguria, no autopsy
16	69, F	Panc.	Resected	8	38	Resection portal vein and vein graft	1	Hemorrhage, disruption of vein anastomosis
18	43, M	Amp.	End-to-side	6¾	7	No	6 hr.	Heart failure, pulmonary edema
22	75, M	Col.	End-to-side	9½	14	Portion of portal vein resected, extension from colon	1	Progressive hypotension, no autopsy
24	33, M	? Col.	End-to-side	9½	10	Portion of portal vein resected	5	Thrombosis superior mesenteric vein
25	59, F	St.	Resected	5½	4	Extension to stomach	42	Disruption gastroenterostomy, peritonitis
27	64, M	Panc.	End-to-side	4	3	No	23	Massive hematemesis, no autopsy
28	53, M	Panc.	End-to-side	6½	6	Extension to colon	56	Fever, subhepatic abscess, no autopsy
30	54, F	Panc.	End-to-end	6	11	Resection portal vein and vein graft	7 hr.	Hemorrhage
32	64, F	Panc.	Duct-to-side	11½	10	No	1	Hemorrhage, blood coagulation defect

* Abbreviations: C.B.D., common bile duct; Amp., ampulla of Vater; Panc., head of pancreas; Col., colon; St., stomach.

terior extension and to confirm the diagnosis. At this hospital, frozen section diagnosis from either Vim-Silverman needle[7, 14] or incisional biopsies has been a routine procedure before proceeding with resection. In doing this the area is isolated with laparotomy pads, and the biopsy instruments are discarded on completion of the procedure. After a diagnosis of cancer is returned, the surgeon changes gloves and proceeds with the determination of local operability. The hepatic flexure of the colon is reflected, and the paraduodenal incision is extended inferiorly to mobilize the third duodenum. The superior mesenteric artery is identified and its freedom demonstrated by inserting a finger between the body of the pancreas and the artery. The presence of cancer in the uncinate process can be determined by bimanual palpation and is usually a contraindication to resection.

Cattell[4] has described a maneuver to demonstrate freedom of the portal vein. The hepatic artery is defined by palpation. The peritoneum over it is incised, and the gastroduodenal artery is ligated at its origin and divided. Upon retraction of the distal end of the gastroduodenal artery inferiorly, the portal vein is identified behind it. A finger is slowly insinuated between the anterior surface and the vein and the body of the pancreas. This separation proceeds easily if there is no involvement of the portal vein. Palpation with one hand behind the pancreas will help to demonstrate the proximity of the tumor to the vein.

Upon completion of these steps the surgeon may proceed being confident that he will not encounter tumor or dangerous fixation of vessels. He has not been committed to resection at any point. With the exceptions of the biopsy and search for lymph node metastases, each step has facilitated the subsequent resection.

The resection and reconstruction. The surgeon undertaking pancreaticoduodenectomy finds himself faced with resection of a portion of the biliary tract, the stomach and the head of the pancreas. Each of these areas of resection and their method of reconstruction has produced postoperative complications in this series. In the majority, the gall bladder was left undisturbed, but only in case 4 did its presence result in complications. This patient returned to the hospital 7 months after resection with high fever and a tender, fluctuant area of the right upper quadrant of the abdomen near an old drain site. Upon incision, dark bile and a number of black, faceted gallstones drained forth. The fever subsided rapidly and the bile fistula closed slowly.

Had the patients in this series survived longer, the incidence of inflammatory disorders of the retained gall bladder might have increased. On the other hand, Waugh and Giberson[15] report only 1 case of cholecystitis on follow-up of 68 individuals in whom the gall bladder was undisturbed at resection. Another argument in favor of resection of the gall bladder is that it allows the common bile duct to be divided above the entrance of the cystic duct and adds a greater margin to this pathway of direct invasion of tumor.

Surgeons were equally divided in this series as to the performance of end-to-end or end-to-side anastomosis of the common bile duct to the intestine. Neither type of anastomosis seemed especially prone to disruption. Since the common bile duct is usually quite distended, either type of anastomosis can be performed with ease. The choice will depend primarily on whether the end of the intestine is to be used for another anastomosis. In the unusual case with a bile duct of normal size, most surgeons prefer an end-to-side union.

The method used by the surgeon in dealing with the pancreatic remnant seemed to influence the mortality and morbidity. In 3 operations, the cut end of the pancreas was closed; 2 of these patients died postoperatively and the other survived a pancreatic fistula. Of the 2 patients who died, one had a proved pancreatic fistula and the other had sepsis from an unknown source.

Twenty-eight patients in this series had anastomoses performed between the pancreatic remnant and the intestinal tract. The anastomosis was pancreatic end-to-side of the intestine in 17 cases with 9 deaths and one nonfatal pancreatic fistula. Of the 9 deaths, 1 (case 7) could be definitely related to a disruption of the anastomosis. The anastomosis was end-to-end in 4 operations with 2 fatalities. Although the fatalities could not be definitely related to a disruption of the anastomosis, one of the 2 survivors had a proved pancreatic fistula. Child[5] and the Mayo Clinic group[15] prefer this method of anastomosis. Seven patients had a mucosa-to-mucosa anastomosis between the pancreatic duct and the jejunum. One of these patients died of causes not related to the method of anastomosis; none of the other persons died or developed pancreatic fistulae.

Cattell[4] has described the technique of pancreatic duct anastomosis in detail. The argument is frequently advanced that the pancreatic duct is too small for anastomosis. On the other hand, the anastomosis has been performed in dogs at this institution[1] and elsewhere[9] without disruption and with demonstration of patency in a high percentage of cases. The dog's pancreatic duct is approximately 2 mm. in diameter.

Two patients had hematemesis in the immediate postoperative period, leading to the death of one of them. Another patient (case 23) had severe hematemesis and proved marginal ulceration at the gastroenterostomy 30 months after resection. It would seem desirable to resect enough stomach to abolish the antral stimulus to acid secretion. The stomach was joined to the intestine proximal to the pancreas and bile duct in only 3 persons (cases 10, 21 and 32). One individual (case 21) survived 19 months without evidence of gastrojejunal ulceration; the other 2 patients died postoperatively. Although this arrangement theoretically allows a portion of jejunum to be bathed in acid secretions, it is recommended by Cattell,[3] who does not report difficulty with ulceration near the gastrojejunostomy. In general, surgeons at this hospital have preferred to arrange the biliary tract, pancreatic remnant and stomach in that order from proximal to distal as preferred by Rhoads *et al.*[13]

The operative team. Only a brief survey of the surgical literature is required to establish that the best results have come from centers where pancreaticoduodenectomy has been the exclusive regard of a single expert surgeon. The surgical resident who has performed a subtotal gastrectomy, splenectomy and vagectomy may be quite competent to perform a total gastrectomy without supervision. On the other hand, if he undertakes resection of the head of the pancreas, he frequently finds himself in unfamiliar anatomical planes, confronted with a number of sources of catastrophe and without a definite plan of action. Even the experienced surgeon may be ill prepared to undertake pancreaticoduodenectomy if he has not given attention to the experience of others and has not conceived a stepwise procedure to accomplish his objectives.

It is suggested that surgical teaching services establish an operative team headed by a surgeon who has made a study of pancreatic resection. A case in point has been the experience at this hospital with pelvic exenteration, another operation in unfamiliar planes and with peculiar technicalities. Through the efforts of a small nucleus of surgeons[2] the mortality has been lowered from 28 per cent to the range of 5 per cent. These surgeons, in turn, have been able to instruct junior staff surgeons in the peculiarities of the operation so that they have been able to perform the operation with low mortality. At present, an interested resident may become capable of performing the operation before he finishes his last year of training. A similar approach to pancreaticoduodenectomy would seem desirable.

SUMMARY

In the past decade 34 persons underwent resection of the head of the pancreas for malignant neoplasms at Barnes Hospital. Of 28 individuals who had a standard form of pancreaticoduodenectomy, 11 died (39 per cent). Of 6 individuals who had more radical procedures, 5 died. Sepsis was the most frequent cause of mortality and morbidity.

The most important technical fault was the tendency of the surgeon to become committed to pancreatic resection before he had determined whether the tumor extended to the limits of resection. The influence of a number of factors in surgical technique on mortality and morbidity is presented.

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THE DIAGNOSIS AND SURGICAL CLOSURE OF THE OSTIUM SECUNDUM ATRIAL SEPTAL DEFECT: A CLINICAL STUDY*

CHARLES L. ROPER, M.D., AND KIRKLEY R. WILLIAMS, M.D.†

St. Louis, Missouri

The direct open heart approach for the correction of intracardiac defects has supplanted closed techniques.[1–3, 6, 7] Hypothermia and heart-lung pumps used separately or in combination have enabled the surgeon to successfully repair, with reasonable safety, most of the intracardiac lesions.

Proponents of the various open techniques have shown that excellent results can be obtained with the closure of ostium secundum atrial septal defects by one specific method, *i.e.*, hypothermia or extracorporeal support. We feel, however, that adherence to one technique is unnecessary for the closure of ostium secundum defects if precise preoperative diagnostic studies are obtained. To substantiate this belief an analysis of our first group of patients was undertaken.

EMBRYOLOGIC CONSIDERATIONS

During the fifth to eighth embryonic week, separation of a previously common atrium into two distinct chambers occurs.[9] An early appearing septum primum together with a later arising septum secundum are responsible for the division of the common atrium. Complete separation of the right and left atria does not normally occur until after birth, when physiologic closure of the foramen ovale by the valvula foraminis ovalis is attained. Subsequent fibrous fusion of the valvula to the septum takes place in approximately 75 per cent of all persons. In the remaining 25 per cent of persons, "probe patency" of the foramen ovale persists.[10] The term "valvular competent, patent foramen ovale" has also been applied to this condition.[5] These interatrial communications are not usually considered to be abnormal.

If however, an anomalous growth pattern exists in the development of either septum, then a true postnatal interatrial septal defect will be present. Thus, a secundum type of defect may result from excessive resorption of the septum primum in the presence of a fully developed septum secundum or by developmental arrest of the septum secundum itself.

CLASSIFICATION OF DEFECTS

All atrial septal defects may be divided into 4 general categories which include (1) the common atrial type, (2) the septum secundum type, (3) the septum primum type and (4) the atrioventricularis communis type. Of course, all of these interatrial defects may have associated anomalous venous drainage and their intracardiac abnormalities.[4] Although other authors have subscribed to various classifications, no further delineation of categories is necessary for the presentation of our clinical material.

PATIENT ANALYSIS

A 42-year-old white woman with cardiac decompensation and mild pulmonary hypertension was the first patient to undergo open heart surgery for the closure of an ostium secundum interatrial septal defect at this institution. In the ensuing 3-year interval, 51 other patients had similar procedures performed for the closure of an ostium secundum septal defect. This series of consecutive patients does not include those cases in which any type of anomalous venous drainage was found. A considerable number of such patients who had an ostium secundum defect in combination with the various types of anomalous venous drainage were seen and successfully operated upon during the same period. The majority of these operative procedures were performed by Dr. Thomas H. Burford, the Chief of Service. It is of significant interest, however, to note that the series also includes all service cases operated upon by his associates and senior residents of the Thoracic and Cardiovascular Service at Barnes Hospital.

Age distribution. The oldest patient undergoing operation was a 53-year-old woman, and the youngest was a 4-year-old boy. There were 24 children and 28 adults in the total group.

Sex incidence. There were 29 female patients and 23 male patients encountered in the series.

* From the Thoracic and Cardiovascular Service, Barnes Hospital, St. Louis, Missouri.
† Fellow in Thoracic Surgery.

This small ratio of females to males is unusual in that most reports reveal from a 2:1 to as high as a 4:1 female to male ratio.

Symptomatology. Out of 24 children 16 were apparently asymptomatic, whereas only 4 adults had no symptoms. Exertional dyspnea was encountered in almost 50 per cent of all patients. Only 20 per cent of the total group had noted abnormal cardiac palpitations. Of the entire group 25 per cent had been digitalized for evidence of congestive heart failure before their admission for diagnostic work at this institution; 20 per cent of the patients revealed easy fatigability. Intermittent cyanosis was mentioned by 3 patients but confirmed in only 1 instance. Only 10 per cent of all cases revealed a history of frequent respiratory infections. Of particular interest was the occurrence of subacute bacterial endocarditis in only 1 patient. This latter finding substantiates both clinical and experimental reports concerning the rarity of this complication with the ostium secundum interatrial septal defect.[8]

Heart murmurs. A systolic murmur of grade III to IV intensity was present in every patient. Typically, it was best heard along the left sternal border in the second and third intercostal spaces. In few instances other concomitant murmurs were audible. A thrill was noted in 15 cases.

Electrocardiography. In only 1 instance was the electrocardiogram interpreted as being within normal limits. The remaining tracings all revealed right ventricular enlargement with incomplete or complete right bundle branch block. Atrial fibrillation was seen on 3 tracings and atrial flutter was present on 2 other electrocardiograms.

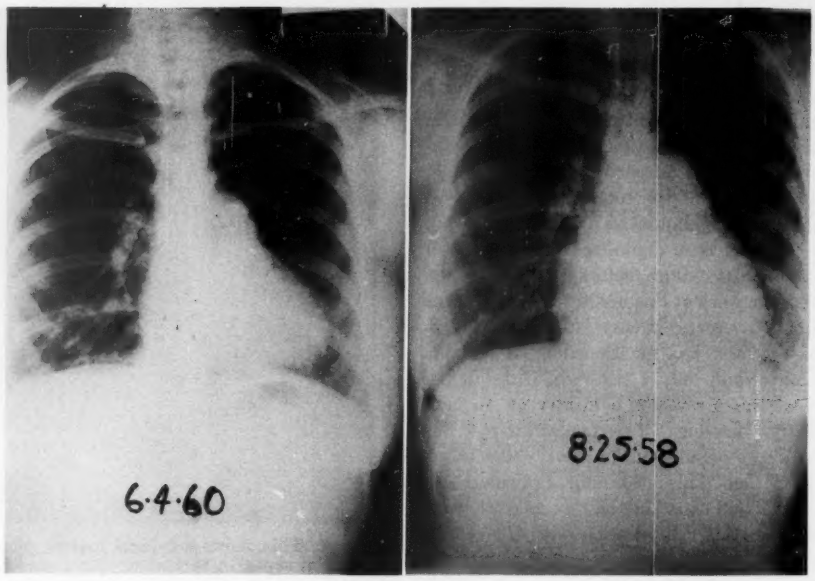
Roentgenologic findings. The classical roentgenologic findings characteristic of an atrial septal defect were present to some degree in each of our patients. Right ventricular enlargement, right atrial dilation, main pulmonary artery prominence and increased pulmonary vascularity typify this defect. Aortic narrowing was rarely noted.

Cardiac catheterization and angiocardiography. Cardiac catheterization studies were carried out preoperatively upon all patients in this series. This procedure together with selective angiocardiography was performed under general anesthesia in all children and by means of local anesthesia in the adult group. At the time of catheterization, a left to right shunt was found in all patients and the catheter was passed through the defect into the left atrium in 60 per cent of the procedures. In an attempt to delineate the size and position of the defect, selective angiocardiography was performed in 17 instances. There is little question that angiocardiography is invaluable in helping to select those patients whose defect closures may be more judiciously carried out by means of extracorporeal support rather than under hypothermia. Before the frequent use of angiocardiography in this institution, 3 patients who were thought to have ostium secundum type defects, but in whom the primum type defects were found, were operated upon under hypothermia. In 2 instances successful closure of the defect was accomplished. The third patient did not have complete closure of her defect and was subsequently reoperated upon using extracorporeal support.

FIG. 1. This shows a typical ostium secundum interatrial septal defect as demonstrated by angiocardiography with the catheter in the left atrium.

OPERATIVE TECHNIQUES

Of the 52 patients undergoing operation, 38 have had closure of their ostium secundum defects by the technique of hypothermia. The remaining 14 patients were operated upon by means of extracorporeal support using the Mayo modified Gibbon type pump oxygenator. The criteria for the selection of this latter group of patients have included: (1) marked cardiomegaly, (2) a



FIGS. 2 AND 3
These reveal the pre- and postoperative cardiac silhouettes of a 19-year old woman who underwent open heart surgery for the closure of a secundum type defect.

large, low lying defect whose inferior margin is not clearly delineated by angiocardiography, (3) a large shunt with pulmonary hypertension and (4) any equivocal evidence suggesting the presence of associated intracardiac defects.

The technique of hypothermia used in these patients is somewhat similar to that described by Swan and associates.[11]

The lowering of body temperature was achieved by ice water immersion. The range of temperature varied from 28 to 33°C. Most cases, however, were operated upon at temperatures ranging between 30 to 31°C. Both sternal splitting and anterior bilateral thoracotomy incisions were used. All patients were operated upon in the usual supine position. Although a regular atriotomy incision was used in most instances, in 5 cases, closure of the defect was accomplished through the right auricular appendage which was subsequently closed by means of a previously placed purse-string suture. A continuous 3-0 black silk suture was used to approximate the edges of the defect in all instances. Additional, interrupted black silk sutures were used to reinforce the suture line as needed. In no instance was it necessary to use a second period of inflow occlusion. Inflow occlusion time ranged from 3 to 7.5 minutes, the average occlusion time for all cases being 4.6 minutes.

In the 14 patients whose defects were closed by assistance with extracorporeal support, the technique of defect closure was essentially the same as that described previously. In all instances, however, the usual atriotomy incision was performed. Regardless of the size, no patch was needed for closure of any defect. Time on bypass ranged from 20 to 29 minutes, the average bypass time for all cases being 23 minutes.

MORTALITY AND MORBIDITY

There was one death very early in this series of patients. This patient was a 40-year-old man with severe pulmonary hypertension and a right to left shunt. He died on the day of the operation, which had been performed under hypothermia. In this group of patients a serious postoperative arrhythmia has rarely occurred. We feel that this, in part, has been due to the routine use of digitalis pre- and postoperatively. Two patients developed overt right heart failure which responded to increased daily maintenance doses of digitalis. One 37-year-old woman, now 14 months postoperative, has developed a mild cyanosis and

clubbing. Recatheterization and angiocardiography have been performed and no evidence of an intercardiac right to left shunt has been found. A 28-year-old woman, now 3 years postoperative, has been found to have a small residual shunt by catheterization performed elsewhere, although her heart size had decreased and no murmur was heard at the time of her last postoperative visit to Chest Service.

SUMMARY

1. Since initiation of open heart surgery at Barnes Hospital there has been one death among the first 52 patients operated upon for the closure of an ostium secundum type interatrial septal defect. Cases in which any type of anomalous venous drainage was encountered have not been included in this analysis.

2. Cardiac catheterization and, more particularly, selective angiocardiography have been invaluable in helping to select those patients who should be operated upon using extracorporeal support as opposed to hypothermia.

3. Extracorporeal support has been used for 14 patients, and hypothermia has been used for the remaining 38 patients in this reported series. At the present time, it is still our feeling that the technique of hypothermia is the method of choice in carrying out the closure of an uncomplicated ostium secundum interatrial septal defect. The criteria for the selection of patients to be done with the assistance of extracorporeal support has been outlined.

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ERRATUM AND ADDENDUM

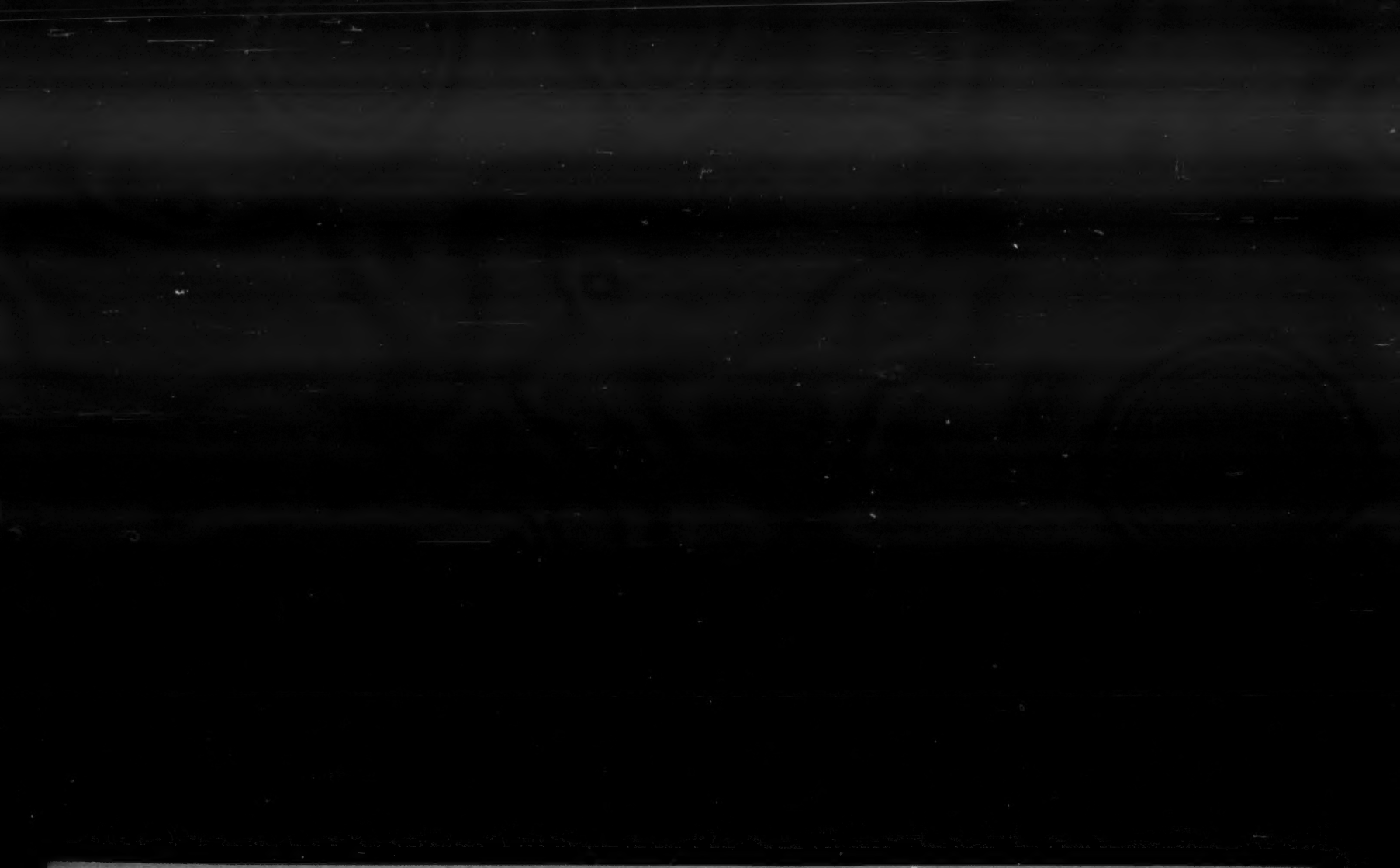
In the November 1960 issue, Vol. 26, No. 11, page 738: Edward R. Munnell, M.D., Carlos R. Mota, M.D., and William Best Thompson, M.D., "Iatrogenic Arteriovenous Fistula: Robert of a Case Involving the Superior Mesenteric Vessels," please note the following corrections:

Footnote, page 738, should read: Presented before the 12th Annual Assembly of the Southwestern Surgical Congress, Las Vegas, Nevada, March 28–31, 1960.

Under *Case Report*, line 3, page 738, date should read: October 1958.

After *Summary*, page 743, name should read: Dr. Edward R. Munnell.

ADDENDUM

Three additional cases of arteriovenous fistula have been reported since presentation of the current case.

1. A case of arteriovenous fistula following intervertebral disc surgery. Sze, K. D., Tsuji, H. K., Schabinger, R., Kneisel, J., and Cooper, P.: Arteriovenous fistula between the common iliac vessels. A. M. A. Arch. Surg., *80:* 90, 1960.
2. Another fistula following nephrectomy is reported. Harbison, S. P., Gregg, F. J., and Gutierrez, I. Z.: Arteriovenous fistula following nephrectomy. Ann. Surg., *152:* 281, 1960.
3. An interesting postoperative arteriovenous aneurysm of the mesentery of the small bowel was reported 2 months after the case of this report was presented. Movitz, D., and Finne, B.: Postoperative arteriovenous aneurysm in mesentery after small bowel resection. J. A. M. A., *173:* 42, 1960.